FORMULATION AND EVALUATION OF GLICLAZIDE MICROSPHERES

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THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY
Chennai-600032

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Submitted by
REG. NO: 261210601

Under the Guidance of

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This is to certify that the Dissertation entitled **"FORMULATION AND EVALUATION OF GLICLAZIDE MICROSPHERES"** submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, is a bonafide project work of **Reg. No: 261210601,** in the Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Tiruchengode for the partial fulfillment for the degree of Master of Pharmacy under the guidance of **R. NATARAJAN, M.Pharm., (Ph.D.)** Swamy Vivekanandha College of Pharmacy, Tiruchengode.

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This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

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CONTENTS

1.ABSTRACT

The objective of the present study was to develop Gliclazide microspheres in order to achieve an extended retention in the upper GIT. Which may result in enhance the absorption and improve the bioavailability. The microspheres were prepared by emulsion solvent diffusion-evaporation method using different ratios of rate controlling polymer poloxamer 407, Gliclazide is used in each formulation at constant ratio. The mixture of dichloromethane and ethanol at ratio of (1:1), with tween 80 as the surfactant. The prepared microspheres were evaluated for percentage yield, particle size, entrapment efficiency, shape and surface characterization, in vitro dissolution studies and drug release mechanism was interpretated by kinetic model. The effect of polymer concentration on these parameters was investigated. The studies revealed that increase in concentration of hydrophilic non-ionic polymer (Poloxamer 407) increased the drug release from the microspheres. The formulation F6 (Gliclazide:poloxamer 407 is 1:6) was selected as best formulation, and it follows zero order drug release with 89.36% entrapment efficiency, 98.16% drug content, 93.85% *In-vitro* drug release at 12^{th}hour.

2. INTRODUCTION

Oral drug delivery is the most widely used route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most popular, convenient and safe due to ease of administration, patient acceptance, and cost-effective manufacturing process. [1]

Most of the pharmaceutical products designed for oral delivery are conventional drug delivery systems. Problem encountered with conventional dosage forms are: drugs with short half life require frequent administration, which may increase chance of missing dose of drug leading to poor patient compliance. Fluctuations in drug plasma concentration this may accumulate side effects. [2, 3]

In order to overcome the drawbacks of conventional drug delivery system, several technical advancements have led to development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[4]

CONTROLLED DRUG DELIVERY SYSTEM [5]

Controlled release systems include any drug delivery systems that achieve slow release of drug over an extended period of time.

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time.

However, such oral drug delivery devices have a physiological limitation of gastric retention time (GRT). Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system (DDS) in the absorption zone i.e. stomach or upper part of small intestine, this leads to diminished efficacy of the administered dose.

To overcome these limitations, several approaches being proposed to prolong the GRT include microspheres; mucoadhesive systems; high-density systems; modified-shape systems and other delayed gastric emptying devices.

Microspheres are among the several approaches that have been developed to increase the GRT of dosage forms. This Gastro retentive microspheres drug delivery system have a bulk density lower than that of gastric fluids and thus remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time .While the system is releasing on gastric contents, the drug is released slowly at a desired rate from the system.

Both single and multiple unit systems have been developed. Single-unit systems are unreliable in prolonging the GRT owing to their 'all-or-nothing' emptying process and, thus, may result in high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple-unit particulate dosage forms (e.g. microspheres) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing the inter subject variability in absorption and risk of local irritation.

Various multiple-unit microspheres systems have been developed in different forms and are based on various principles, such as air compartment multiple-unit system; micro particles based on porous carriers; hollow microspheres ; oil-entrapped gel beads.

Various natural, semi synthetic and synthetic polymers have been used in the development of microspheres to entrap the drug. As a microsphere polymer poloxamer has been investigated extensively because it forms gelataneous mass and increase on the gastric contents. And it is non toxic and eliminated easily from the body. Ethyl cellulose (EC) is used as co-polymer which increases the stability of polymer poloxamer, and provides good drug release barrier, it also aids to improve buoyancy. [(6)]

Diabetes

It is a complex metabolic disorder resulting in hyperglycaemia. Hyperglycaemia may be attributed to defects in pancreatic β- cells, insulin secretion, hepatic glucose output, glucose uptake of peripheral tissues and immune function. Polyurea (frequent urination) and polyphagia (increased hunger) are the symptoms of diabetes. [7]

Diabetes mellitus is classified into two types, insulin dependent diabetes mellitus (type-I) and non insulin dependent diabetes mellitus (type-II). Type-I diabetes occurs due to the cellular mediated autoimmune destruction of the β- cells of the pancreas. Type-II occurs at past middle age and common disease, in this there is no destruction of β- cells. Type-II is 95% prevalence and type-I is 5% prevalence among diabetes [8].

The world wide prevalence of diabetes in 2013 was approximately 6.6% and estimated to grow to 7.8% by 2030. In India diabetes was 5% prevalence in urban areas and 2.7% prevalence in rural areas. 50.8 million people were affected in 2013 and also reported that in India 87 million people will be affected in 2030. [9]

Gliclazide:-

Gliclazide is a second-generation hypoglycaemic sulfonyl urea that can acutely lowers the blood glucose level in humans by stimulating the release of insulin from pancreas and is typically prescribed to treat type-II diabetes mellitus. The drug is selected as model for designing controlled release because of its short biological half-life (3.4±0.7 h) necessitates that it can be administered 2 or 3 doses with 2 to 8 mg per day, and is easily absorbed from GIT. [10]

3. REVIEW OF LETERATURE

Diabetes is a condition in which pancreatic beta cells does not produce insulin or impaired release of insulin due to inadequate or defective insulin receptors, and it also developed if insulin is not utilized by body cells.

It is also a disorder of carbohydrate, protein and fat metabolism results an imbalance between insulin ability and insulin need. A person with uncontrolled diabetes is unable to transport glucose in to fat and muscle cells, as a result, the body cells are starved and the breakdown of fat and protein is increased. (11)

It is characterized by varying or persistent hyper glycaemia and glucosuria, hyper lipedimia, negative nitrogen balance. Polyurea (frequent urination) and polyphagia (increased hunger) are symptoms of diabetes. (12)

TYPES OF DIABETES (13)

1) TYPE-I DIABTES (IDDM)

2) TYPE-II DIABETS (NIIDM)

Type-I Diabetes:-

Type-I diabetes is also called as insulin dependent diabetes mellitus (IDDM), which accounts for only 5-10% of peoples with diabetes mellitus have this type of diabetes. It is characterized by destruction of pancreatic beta cells that means absolute lack of insulin, an elevated body glucose, and break down of body fats and proteins

It is sub divided into two types:

- Type IA: Immune mediated diabetes.
- Type IB: Idiopathic diabetes.

Type IA: 95% of type-I diabetes having Type IA. It is characterized by auto immune destruction of beta cells. This type is also called juvenile diabetes; occur more commonly in young people but may occurs at any age.

Type IB: Only a small number of people with type-1 diabetes fall into this category. It is strongly inherited. People with this have episodic ketoacidosis due to varying degree of insulin deficiency with periods of absolute insulin deficiency that may come and go.

Type-II Diabetes:-

Type-II diabetes is also called as non insulin independent diabetes (NIIDM). This was previously called "adult-onset diabetes" because in the past it was usually discovered after 40 years age. However, with increasing levels of obesity and sedentary lifestyle, this disorder is sometimes found even in children's so the term "adult-onset" is no longer used. (11).90-95% of diabetes comes under this category. In this type of diabetes, either the pancreas produce reduced amount of insulin, or body cells do not respond to insulin, sometimes both. They having insulin resistance and usually have relative (rather than absolute) insulin deficiency. They don't need insulin treatment to survive.

There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

There are other less common types of diabetes called gestational diabetes, prediabetes.

Gestational diabetes [14]

Pregnant women who have never had diabetes before but having high blood glucose levels during pregnancy are said to have gestational diabetes. Based on recently announced diagnostic criteria for gestational diabetes, it is estimated that gestational diabetes affects 18% of pregnancies. The exact cause for this is not known. This may lead to complications during pregnancy, labour and delivery.

Pre diabetes [15]

When a person's glucose level in the blood is above normal limits, but it is not enough for yielding results in a diabetes test, the condition is called pre-diabetes. Damage to heart and circulatory system can occur during this stage also without getting diagnosed with diabetes. If the patient takes precautionary measures for the control of blood sugar level, then he can prevent or delay the onset of type-II diabetes.

DIAGNOSING DIABETES [16]

Diabetes can be diagnosed in one of three ways:

- Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) and casual plasma glucose (any time of day, regardless of fasting status) of ≥200 mg/dL
- Fasting plasma glucose (after 8 hours or longer of fasting) that is ≥126 mg/dL
- Plasma glucose ≥200 mg/dL 2 hours after ingestion of 75-g oral glucose (2-hour oral glucose tolerance test)

Table- 1

DIAGNOSIS	**FASTING PLASMA**	**2-HOUR ORAL GLUCOSE**
No diabetes	<100 mg/dL	<140 mg/dL
Pre diabetes	100–125 mg/dL	140–199 mg/dL
Diabetes	≥126 mg/dL	≥200 mg/dL

CAUSE OF DIABETES MELLITUS[17]

The reason differs for people with type-I diabetes and those with type-II diabetes. However, the exact mechanisms for development of both diseases are still unknown.

Type-I diabetes causes:-

- Type-1 diabetes usually occurs as a result of the body's immune system attacking the beta cells of the pancreas by mistake.
- This is known as an auto-immune reaction. The immune system destroys or damages the pancreatic cells preventing the production of insulin. The reason why the immune system acts this way is not known exactly.
- There is a genetic risk factor for type-1 diabetes, meaning people who have a family history of diabetes mellitus are more likely to develop an auto-immune reaction.
- Another known cause of type- 1diabetes is a rare condition called pancreatitis, which causes pancreas to become inflamed, resulting in severe damage to the insulin-producing cells.

Type-II diabetes causes:-

Type-II diabetes occurs when the pancreas does not produce enough insulin to take glucose out of blood and into the body's cells, or when the cells develop resistance to insulin. Although the exact cause of type-II diabetes is not fully understood, there are many factors that increase the risk of developing the condition.

These include:

Being overweight or obese:

Type-II diabetes is often linked to obesity, as excess body fat increases the risk of the body's cells becoming less responsive to the effects of insulin. 80% of people who develop type-II diabetes are overweight or obese, have a large waist, and have an inactive lifestyle.

Ethnic origin:

People of certain ethnicities are more at risk of developing type-II diabetes than others. For instance, people of African-Caribbean or South Asian origin and living in the UK are at least five times more likely to develop type-2 diabetes than a person who is white.

Age:

It is largely based on the fact that people usually become less active and gain weight as they grow older. Type-II diabetes is common in people who are over 40 years old. So it is sometimes referred to as maturity onset diabetes. However, in recent years an increasing number of young adults and children have been diagnosed with the disease.

Genetic factors:

Type-II diabetes more likely to develop if one has a close relative such as a parent or sibling who has the disorder.

Pre-diabetes:

People having pre-diabetes may suffer from impaired glucose tolerance (IGT) or impaired fasting glycaemia (IFG). Both these conditions can develop into type-II diabetes if left untreated.

DIABETES SYMPTOMS[18]

The symptoms of diabetes mellitus are generally the same for type-I and type-II diabetes, but in type-I diabetes, these symptoms can develop very quickly compared to type-II diabetes.

The three main symptoms of diabetes are

- Polyuria (the need to urinate frequently)
- Polydipsia (increased thirst and fluid intake)
- Polyphagia (increased appetite)

Other less severe symptoms of diabetes can include:

- Extreme tiredness (fatigue)
- Unexplained loss of weight and muscle bulk
- Itchy skin or yeast infections
- Blurred vision

- Cuts or sores that take a long time to heal
- Tingling or numbness in hands or feet

Nausea, vomiting, temperature or stomach pains may also accompany some of these symptoms in the sudden onset of type-I diabetes.

DIABETES RISKS:-

If diabetes is not controlled, it will cause serious health problems which include cardiovascular disease, chronic renal failure, retinal damage, nerve damage, impotence and gangrene with risk of amputation of toes, feet, and even legs.

Chronic complications:-

Eye Complications: Diabetic retinopathy, cataracts and glaucoma are also more common among diabetics.

Kidney damage: Kidney damage from diabetes is called diabetic nephropathy.

Nerve damage: Nerve damage from diabetes is called diabetic neuropathy.

Acute complications:-

Diabetic ketoacidosis :

Diabetic ketoacidosis is caused by the buildup of acid in blood. Symptoms include nausea, vomiting, and abdominal pain. Without prompt medical treatment, patients can rapidly go into shock, coma, and even death.

Hyperosmolar state: This condition can lead to coma (hyperosmolar coma). A hyperosmolar coma usually occurs in elderly patients with type 2 diabetes. Like diabetic ketoacidosis, a hyperosmolar coma is a medical emergency.

Blood glucose is essential for the proper functioning of brain cells. Therefore, low blood sugar can lead to central nervous system symptoms such as:

- Dizziness
- Confusion
- Weakness
- Tremors

TREATMENT

There is no cure for diabetes, regular treatment can help to control this life-long disease and decrease the risk of other health conditions developing later in life. The type of treatment require depends on the type of diabetes and lifestyle, although it generally involves taking medication, monitoring blood glucose levels, exercising on a regular basis and making changes to diet.

TREATMENT OF TYPE-I DIABETES[19]

Insulin treatments:

Type-I diabetes has regular insulin treatment. There are many types of insulin some are designed to work very quickly but for a short amount of time, while others are designed to last up to a whole day and various methods of taking insulin treatment.

These include:

Insulin injections:-

Daily insulin injections are usually required for people with type-I diabetes. There are two main devices for injecting insulin syringe and injection pen also called as insulin pen.

Insulin pump therapy:-

It is an alternative to insulin injections. It involves the use of small insulin pump that allows insulin to flow into the bloodstream (through a needle which is inserted under the skin of stomach, hips, buttocks, thighs or arms) in controlled manner. This replaces the use of injections, but it will need to keep a close eye on

blood glucose levels to ensure the receiving right amount of insulin. These are accurate, precise and flexible, although they can be hard to access and expensive.

Insulin jet injectors:-

Insulin jet injectors are a relatively new development in diabetes management that delivers insulin into the body without the use of a needle, making them ideal for people who have needle phobia. This type of device works by sending a fine spray of insulin through the skin at a very fast speed using a high-pressure air current. They can be used on the stomach, buttocks or thighs.

OTHER TREATMENTS:

Type-I diabetes may also take a number of medicines to reduce the risk of developing serious complication such as heart disease, stroke and kidney disease. Also need a flu vaccine every year, and a one-off vaccination that protects against some forms of pneumonia and meningitis.

TREATMENT OF TYPE-II DIABETES:-

Treatment of type-II diabetes typically includes taking healthy diet, regular exercise and losing weight if overweight or obese and home blood glucose testing. These help to regulate blood glucose levels. However, it is found that diet and exercise are not enough to keep blood glucose at a healthy level, oral medication is required.

Medicines used to treat type-II diabetes :-

- Sulfonylureas: These drugs stimulate the pancreas to make more insulin.
- Biguanides: These agents decrease the amount of glucose produced by the liver.
- Alpha-glucosidase inhibitors: These agents slow absorption of the starches a person eats. This slows down glucose production.
- Thiazolidinediones: These agents increase sensitivity to insulin.

- Meglitinides: These agents stimulate the pancreas to make more insulin.
- D-phenylalanine derivatives: These agents stimulate the pancreas to produce more insulin more quickly.
- Amylin synthetic derivatives: Amylin is a naturally occurring hormone secreted by the pancreas along with insulin. And helps to reduce fluctuation of blood sugar levels throughout the day, and improves haemoglobin A1C levels.
- Incretin mimetics: Incretin mimetics promote insulin secretion by the pancreas and mimics other blood sugar level lowering actions that naturally occur in the body.
- Insulins: Different types of insulin are available and categorized according to their onset of action and duration.

Examples of rapid-acting insulins

- Regular insulin (Humulin R, Novolin R)
- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)
- Prompt insulin zinc (Semilente, slightly slower acting)

Examples of intermediate-acting insulins

- Isophane insulin, Neutral protamine hagedorn (NPH) (Humulin N, Novolin N)
- Insulin zinc (Lente)

Examples of long-acting insulins

- Extended insulin zinc insulin (Ultralente)
- Insulin glargine (Lantus)
- Insulin detemir (Levemir)

PREVENTION:-

Diabetes can be prevented by changing a person's diet and by having proper exercise. Taking healthy diet, regular physical activity will help to prevent or delay type-II diabetes it is not yet known how to prevent type-I diabetes. Type-II diabetes, however, can be prevented in some cases.

- Control weight to normal or near-normal levels by eating a healthy low-fat, high-fibre diet.
- Regular exercise is crucial to the prevention of type-I diabetes.
- Keep alcohol consumption low.
- Quit smoking.
- If a person has high blood fat levels or high blood pressure, take all medications as directed.
- Lifestyle modifications and certain medications can be used in people with prediabetes to prevent progression to diabetes.
- Diabetic patient should focus on preventing the complications, which can cause serious disabilities such as blindness, kidney failure requiring dialysis, amputation, or even death.
- Drink an adequate amount of water and avoid consuming too much salt.
- The skin should be taken care and keep it supple and hydrated to avoid sores and cracks that can become severely infected.
- Brush and floss the teeth every day. See a dentist regularly to prevent gum disease.
- The feet should be washed and examined daily, looking for small cuts, sores, or blisters that may cause problems later. The toenails should be filed rather than cut to avoid damaging the surrounding skin.

- **DIABETES CONTROL**
  - Avoid sweets completely.
  - Fried and fatty foods should be minimized.
  - Insulin will work properly if overweight is reduced.

- Foods containing more fibre should be taken. This will help to reduce the absorption of glucose into the blood stream, thereby reducing the sugar level in the blood.
- Consumption of egg yolk, mutton and beef should be reduced. Take fish and chicken without skin instead.
- Amount of oil used in a day should not exceed 4 teaspoons.
- Avoid Vanaspathi and Margarine.
- Avoid excessive eating.
- Do not skip exercise.
- Reduce stress and maintain good health.

SULFONYLUREAS [20]

Sulphonyl ureas are oral hypoglycaemics, used in the treatment of type-II diabetes. These are rapidly absorbed after oral administration, onset of action is 1-2 hours and peak reaches in 4-6 hours. They bind strongly to plasma albumin and execrated through urine.

They cross the placenta and stimulate beta-cells to release insulin, causing severe hypoglycaemia at the time of birth. Hence these are contraindicated in pregnancy.

Pharmacology:

Sulphonyl ureas stimulate beta-cells, effective only in the presence of functioning pancreas. The presence of at least 30% beta-cells is essential for their action. They are secretagogues.

(i) Pancreatic effect: Stimulate pancreas to produce more insulin, and increase peripheral utilization of glucose.

(ii) Extra pancreatic effect: - They inhibit gluconeogenesis in liver.

(iii) They also produce post receptor intracellur beneficial effects, and lower the elevated free fatty acid levels.

GLICLAZIDE[21]

gliclazide is an anti-diabetic drug comes under the category of second-generation sulfonylurea, and is very potent. It acts as insulin sensitizer that has been widely used in management of NIDDM. Its half life is 5 hrs, more than 99% bind to plasma proteins, and is mainly excreted through urine remaining through faeces. gliclazide should be administered with breakfast or the first main meal. Recommended dose is minimum 2 mg to maximum 8 mg.

Like glyburide and glipizide, glimepiride is a "second-generation" sulfonylurea agent. gliclazide is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin.

Mechanism of action [22]

The mechanism of action of gliclazide in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin. gliclazide likely binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Membrane depolarization stimulates calcium ion influx through voltage-sensitive calcium channels. This increase in intracellular calcium ion concentration induces the secretion of insulin.

MICROSPHERES [23]

Novel drug delivery systems have several advantages over conventional multi dose therapy recent trends indicate that microparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of factors including the carrier used to form the microparticles and the amount of drug contained in them. Consequently, microparticulate drug delivery systems provide tremendous opportunities for

designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

One such approach is using microspheres as carriers for drugs. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded and enclosed by an intact shell. Microencapsulation is used to modify and delayed drug release form pharmaceutical dosage forms. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a particular drug. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of drugs.

Micro-particles are the polymeric entities falling in the range of 1-1000μm. Micro-particles covering two types of the forms as follows:

(1) Microencapsules : micrometric reservoir systems.

(2) Microspheres : micrometric matrix systems.

Microspheres are matrix systems and essentially spherical in shape, whereas microcapsules may be spherical or non-spherical in shape.

Drug loading and drug release kinetics [24]

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer.

Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc.) heat of Polymerization, agitation intensity, etc. Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug.

The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself. The drugs could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second by pore diffusion mechanism, and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane.[25]

The burst effect is mainly controlled by three factors the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix.

Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.[26]

3.1 REVIEW OF RELEVENT WORK

Satish V et.al [27] in the present study was microspheres of Pioglitazone hydrochloride were prepared for the prolongation of gastric residence time. The microspheres were prepared by emulsion solvent diffusion-evaporation method using ethyl cellulose and HPMC K100M. A full factorial design was applied to optimize the formulation. Results showed that formed microsphere exhibited smooth surfaces with good flow and packing properties, prolonged sustained drug release, remained buoyant for more than 10 hrs, high entrapment efficiency up to 97%w/w. Scanning electron microscopy confirmed the hollow structure with particle size in the order of 190 μm. The studies revealed that increase in concentration of hydrophilic polymer (HPMC) increased the drug release from the microspheres

Shiv Shankar Hardenia et. al [28] In the present research work, ethylcellulose microspheres containing ciprofloxacin were prepared and evaluated for in-vitro performance of ciprofloxacin. Ciprofloxacin microspheres containing ethylcellulose were prepared by emulsion solvent diffusion evaporation method. The surface morphological characteristics of ethylcellulose microspheres were investigated using scanning electron microscopy. The polymer ratio, stirring speed and the temperature affected the particle size, shape and surface morphology of the microspheres. The in-vitro drug release was carried out using USP paddle type dissolution rate test apparatus in 0.1N Hcl dissolution medium at 291nm. It was found that drug release from the formulations was different at different concentrations of polymers and different RPM and temperature. The best cumulative release was achieved after 24 hrs i.e. 91.6%. The Mucoadhesive property of the ethylcellulose microspheres was evaluated by in-vitro wash off test. The microspheres exhibited 75% mucoadhesion and showed good drug entrapment efficiency. By, above results it was concluded that ethylcellulose microspheres showed reproducible results, with good Mucoadhesive properties and good surface morphology.

Syed Shariff Miyan et al [29] In the present investigation was to prepare fast dissolving tablets of a hypoglycemic drug Gliclazide. The solubility of poorly soluble drug was enhanced by preparing solid dispersions of the drug with PEG 6000 in various

concentrations. The optimized solid dispersions (Drug: PEG-6000, 1:2 ratio) were further kneaded with suitable proportions of superdisintegrants such as; Crosscarmellose, Sodium starch glycolate and Cross povidone. Fast dissolving tablets of Gliclazide was prepared by direct compression method. The pre-compressive parameters for the blends and post-compressive parameters for the prepared tablets were evaluated. All formulations showed desired pre and post-compressive characteristics. Short term accelerated stability study was performed for optimized formulation and found no evidence of physical and chemical changes. FT IR study showed no evidence of drug excipient interaction. The optimized formulation was found to be FDT6. It was concluded that fast dissolving tablets of Gliclazide can be prepared by solid dispersions of drug with PEG-6000 and combination of two super disintegrants provide complete and better dissolution within in shorter period of time. Hence effective diabetic treatment anywhere, and anytime particularly for geriatric, pediatric, mentally ill, bedridden and patients who do not have easy access to water .

Richard C O'Briena et al [30] Diabetes is a state of increased oxidant stress and there is evidence that oxidation may play a role in the genesis of complications. Gliclazide, a sulfonylurea hypoglycemic drug, has been shown to possess free radical scavenging properties. This study examined the effects of in vitro supplementation with gliclazide and other sulfonylureas as on low-density lipoprotein (LDL) oxidation and the total plasma antioxidant capacity (TPAC). In a separate study, the effects of 10 months of oral gliclazide therapy on oxidative parameters were assessed in 44 type 2 diabetic patients. Gliclazide, but not glibenclamide, glimepiride, glipizide or tolbutamide, inhibited LDL oxidation and enhanced TPAC. With the addition of 1 μM gliclazide, oxidation lag time increased from 53.6±2.6 to 113.6±5.1 min ($p<0.001$), and TPAC increased from 1.09±0.11 to 1.23±0.11 mM ($p<0.01$). Administration of either modified release or standard gliclazide to type 2 diabetic patients resulted in a fall in 8-isoprostanes, a marker of lipid oxidation, and an increase in the antioxidant parameters TPAC, SOD and thiols. These studies show that gliclazide possesses antioxidant properties that produce measurable clinical effects at therapeutic doses.

Jacob Shiny et al [31] In the present study was to develop a novel 1 month depot paclitaxel (PTX) microspheres that give a sustained and complete drug release. PTX loaded microspheres were prepared by o/w emulsion solvent evaporation technique using the blends of poly(lactic-co-glycolic acid) (PLGA) 75/25, polycaprolactone 14,000 and polycaprolactone 80,000. Fourier transform infrared spectroscopy was used to investigate drug excipient compatibility. Compatible blends were used to prepare F1-F6 microspheres, the process was characterised and the optimum formulation was selected based on the release. Optimised formulation was characterised for solid state of the drug using the differential scanning calorimetry (DSC) studies, surface morphology using the scanning electron microscopy (SEM), *in vivo* drug release, *in vitro in vivo* correlation (IVIVC) and anticancer activity. Anticancer activity of release medium was determined using the cell viability assay in Michigan Cancer Foundation (MCF-7) cell line. Blend of PLGA with polycaprolactone (Mwt 14,000) at a ratio of 1:1 (F5) resulted in complete release of the drug in a time frame of 30 days. F5 was considered as the optimised formulation. Incomplete release of the drug resulted from other formulations. The surface of the optimised formulation was smooth and the drug changed its solid state upon fabrication. The formulation also resulted in 1-month drug release *in vivo*. The released drug from F5 demonstrated anticancer activity for 1-month. Cell viability was reduced drastically with the release medium from F5 formulation. A 100% IVIVC was obtained with F5 formulation suggesting the authenticity of *in vitro* release, *in vivo* release and the use of the formulation in breast cancer.our study, it was concluded that with careful selection of different polymers and their combinations, PTX 1 month depot formulation with 100% drug release and that can be used in breast cancer was developed.

Takeshi Morirero et al[32] Microspheres of biodegradable polymers were evaluated as a potential controlled-release drug-delivery system in the vitreous. The microspheres were prepared with polymers of poly(lactic acid) or co polymcrs of glycolic acid and lactic acid. The release of 5-fluorouracil (5-FU) from the microspheres was studied in vitro. Poly(lactic acid) microspheres released 70-85% of total 5-FU over 7 days. Microspheres of polymers with a smaller molecular weight released the drug more rapidly. Co polymcr microspheres released 98% of 5-FU over 2 days. The rate of drug

release was controllable by changing the molecular weight of the polymers or using a matrix of copolymer. The intravitreal kinetics of the microspheres were studied in ten rabbits in vivo. A suspension of microspheres was injected into the vitreous cavity of five normal eyes and five vitrectomized eyes. By 48 ± 5.2 days after injection, the microspheres disappeared from the vitreous cavity in the five normal eyes. Clearance from the vitreous cavity was accelerated in the five rabbits that underwent vitrectomy (14 ± 2.4 days; $P < 0.001$). No difference was found in the b waves of electroretinograms before and after injection of the microspheres. The histologic study showed no abnormal findings as a result of the injection. These results suggested that microspheres of biodegradable polymers may be a potential delivery system for the controlled release of drugs in the vitreous.

L.Sambath et al [33] in the present study For a quality formulation, various formulation parameters that play a crucial role are aqueous solubility; stability at ambient temperature and humidity, photo-stability, compatibility with solvents etc. Among all these, Solubility is the most important property for developing formulations. The present study is an attempt to improve the solubility and dissolution rate using solid dispersion of a poorly soluble drug Gliclazide by using Soluplus as carrier material to enhance the solubility as well as dissolution rate. Four different formulations were prepared using hot melt extrusion technique in different ratios i.e., 1:1, 1:2, 1:3 and 1:4 were further characterized by FTIR, DSC, and XRD analysis. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. DSC studies showed that the drug was in amorphous state completely entrapped by the polymer. XRD studies showed decrease in the peak intensity or absence of peaks which indicated the amorphous nature of gliclazide in solid dispersions. All the formulations showed a marked increase in drug release with the increase in the concentration of soluplus when tested for their in vitro studies. Formulation SD4 showed the desired release with a cumulative release of 95% in 50 mins when compared to the pure drug, Physical mixture. Hence, soluplus look to be a promising carrier to improve the solubility of poorly soluble dr.

NP Sapkal et al [34] In the present study Gliclazide has been found to form inclusion complexes with β- cyclodextrin (β-CD) in solution and in solid state. The present study was undertaken to determine a suitable method for scaling up gliclazide-β-CD inclusion complex formation and to evaluate the effect of some parameters on the efficiency of complexation. Method: The solid inclusion complexes of gliclazide and β-cyclodextrin were prepared at a molar ratio of 1:1 and 1:2 by mixing, kneading, and coprecipitation methods both on small and large scales. The effect of parameters such as kneading time and temperature on complexation was also studied. Characterization was performed using infrared spectroscopy, X-ray diffractometry, and dissolution studies. In vitro release studies were carried out in phosphate buffer (pH 6.8). All the methods of preparation of complexes were found to be useful in increasing the solubility of gliclazide except mixing method where the rise in solubility was not significant. Both kneading and co-precipitation methods in 1:2 molar ratios were found to be equally effective in improving the solubility of gliclazide. The formation of inclusion complexes was evident in these formulations as shown by IR and XRD studies. But when carried out on a large scale, co-precipitation method was found to be more tedious and time-consuming than kneading method. Moreover percent recovery of complexes in the kneading method was found to be 98.76% as compared to 92.05% in case of co-precipitation method. Drug content studies, IR spectroscopic studies, X-Ray diffractometry studies and in vitro dissolution study data indicated that inclusion complexes prepared by kneading method in 1:2 molar ratios were suitable for improving the solubility of gliclazide. The same formulation was prepared at large scale and optimum formulation conditions were establishe

Sudarsan Biswal et al [35] in the present study Gliclazide is an anti-diabetic drug that is poorly soluble in water. This paper describes an approach to improve the dissolution rate of gliclazide by using solid dispersions (SDs) in polyethylene glycol 4000 (PEG 4000). The phase-solubility behavior of gliclazide in the presence of various concentrations of PEG 4000 in 0.1 N HCl at 37 °C was obtained. The solubility of gliclazide increased with increasing amounts of PEG 4000 in water. The Gibbs free energy (ΔGotr) values were all negative. The solid dispersions were prepared with a

solvent-melting method using different concentrations of PEG 4000. X-ray diffraction, infrared spectroscopy, and DSC were used to examine the physicochemical characteristics of solid dispersions of gliclazide and PEG. The dissolution rate of gliclazide in SDs with PEG 4000 was enhanced. The FTIR spectroscopic studies showed the presence of intermolecular hydrogen bonding between gliclazide and PEG 4000 in the solid state. The DSC and XRD studies indicate the amorphous and microcrystalline states of gliclazide in SDs with PEG 4000.

Mahendra Labana et al [36] In the present work, modified release gliclazide once a daily tablet were designed for non-insulin dependent diabetes for better patient compliance by direct compression method, HPMC was used as polymer, Dibasic calcium phosphate and Maltodextrin as binder for direct compression. Estimation of MR Gliclazide in the prepared tablet formulations was carried out at 226 nm in phosphate buffer pH 7.4. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, in vitro dissolution time. for in vitro drug release pattern in pH 7.4phosphate buffer and short-term stability (at 40ºC/ 75% RH for 3 months) and drug excipient interaction (IR spectroscopy) were studied. Short-term stability studies on the promising formulations indicated that there are no significant changes in drug content and in vitro dissolution time.

Sharmi islam et al [37] In this study solid dispersion (SDs) of gliclazide were prepared by solvent evaporation technique using poloxamer 407 as carrier. Drug carrier weight ratio were 1:1, 1:3 and 1:5. Physical mixtures of the same ratio were also prepared for comparison. The solid dispersions were investigated for drug loading and dissolution behavior and were found effective to enhance the solubility of gliclazide in dissolution medium significantly. Evaluation of the properties of the SDs was also performed by using Fourier-transform infrared (FTIR) spectroscopy and X-ray diffraction (XRD) studies. The FTIR spectroscopic studies showed the stability of gliclazide and absence of interaction between gliclazide and poloxomer 407. The XRD studies indicated the amorphous state of gliclazide in SDs. Dissolution data of SDs were compared by using both model dependant and model independent techniques. No significant difference in % DE (dissolution efficiency) was found among the SDs. But the drug release rate from

SDs differs from that of physical mixture. So, solid dispersion technique may be an effective way to enhance dissolution rate of gliclazide.

Sharma GS et al [38] in the presents tudy was studied Gliclazide is a second generation sulphonyl urea with poor aqueous solubility. The aim of the present investigation is to increase the aqueous solubility of Gliclazide (Glz) by using Hydroxy Propyl β-Cyclodextrin (HPβ-CD). Solubility studies for Glz and HPβ-CD were performed which reveals that, it follows AL type profile, the solubility of Gliclazide is proportionally increases as the concentration of HPβ-CD increases. Glz- HPβ-CD complexes were prepared in different ratios (1:0.5, 1:0.75, 1:1 molar ratios) by using different preparation techniques (physical mixture, kneading method and solvent evaporation method). FTIR studies were conducted for all the prepared complexes and the results concluded that there were no interactions between Glz and HPβ-CD. Dissolution studies were performed for all the prepared complexes in phosphate buffer of pH 7.4. The results conclude that complex prepared by solvent evaporation method at 1:1 molar ratio has faster dissolution rate when compared with all the other complexes.

S Biswal et al [39] The aim of the present study was to characterise gliclazide solid dispersions (SDs) preparedwith polyethylene glycol (PEG) 8000 and compare them with SDs in PEG 6000. Methods: Gliclazide SDs containing varying concentrations of PEG 8000 were prepared using the fusion – solvent technique, and their phase solubility behavior and dissolution in 0.1N HCl were assessed at 37 oC. The physical state of, and gliclazide-PEG interactions in, SDs and physical mixtures prepared in ratios of 1:1, 1:2 and 1:5 (gliclazide: PEG 8000), respectively, were characterized by x-ray diffraction (XRD), Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). Results: The solubility of gliclazide increased with increasing amount of PEG 8000 in aqueous medium. Gibbs free energy (Go tr) values were all negative, indicating the spontaneous nature of gliclazide solubilisation. Dissolution studies indicated a significant increase in the dissolution of gliclazide when dispersed in PEG 8000. FTIR analysis demonstrated the absence of well-defined gliclazide - PEG 8000 chemical interaction while DSC and XRD studies indicated the amorphous /microcrystalline state of gliclazide in the SDs. Conclusion: In both solid dispersions and

physical mixture, PEG 8000 increases the solubility and dissolution rate of gliclazide. The increased dissolution rate of gliclazide may be due to the formation of microcrystals, increased wettability and dispersibility in systems containing PEG 8000.

Pei-Heng Lai et al [40] To study the potential of Poloxamer 407 as the thermogelling and mucoadhesive polymer for the development of a site-targeting delivery system to enhance the delivery of anti-cancer drugs to the colorectal cancer cells. ***Methods:*** Poloxamer 407 was completely dispersed, with a continuous agitation, in the distilled water. The temperature was then cooled down to 4□., while the agitation continuous, until a clear solution is produced. The cytotoxicity of Poloxamer 407 solution was performed and analyzed by MTT, while its mucoadhesive strength and rheological properties were also measured, as a function of Poloxamer concentrations. ***Results***: In order to confirm whether or not Poloxamer 407 is biocompatible to the target cells, its cytotoxicity against the colorectal cancer was evaluated and the results suggested that it is nontoxic to 5 primary colon cancer cells up to a concentration of 150mg/mL (Fig. 1). The gelation temperature-concentration profile in Fig. 2 indicates that Poloxamer 407. The results in Table 1 indicate that the mucoadhesive strengths of Poloxamer 407 show a temperature-dependent increase, which appears to be related to the increment in the dynamic viscosity and elastic modulus of the polymer. ***Conclusion:*** Poloxamer 407 could be a potential thermogelling and mucoadhesive polymer for the development of a site-targeting colorectal DDS.

T.s.keerthi et al [41] in the Present investigation describes preparation of microspheres by solvent evaporation followed by in vitro characterization of microspheres to evaluate the effect of method of preparation on physical properties and drug release profile of microspheres. The microspheres were found to be discrete, spherical with free flowing properties. The morphology (Scanning Electron Microscopy), particle size distribution, entrapment efficiency and their release profiles were investigated. The yield was found to be maximum in case of solvent evaporation method. The microsphere prepared by solvent evaporation method was found in ranges of 250-50 μm, respectively. The microspheres formulation prepared by solvent evaporation method the drug carrier interactions were investigated in solid state by Fourier Transform

Infrared (FT-IR) spectroscopy study. In vitro drug release rate for A microsphere was found to be sustained over 12 hours. Hence, it can be concluded that the Formulation prepared by solvent evaporation method, has potential to deliver Losartan Potassium in a controlled manner in a regular fashion over extended period of time in Comparison to all other formulations and can be adopted for a successful oral delivery of Losartan potassium for safe management of hypertension.

Meral Yüce Et Al [42] In the present study was Indomethacin-loaded microspheres of ethylcellulose were prepared by the emulsion solvent evaporation technique. The aim of this work was to investigate the influence of process variation inpolymer type via viscosity grades of ethylcellulose N10 and N100, drug to polymer ratio, stirring rate of the propeller and surfactant type on the micromeritic properties of microspheres such as particle size distribution, bulk and tapped density, surface topography, tangent of angle of repose, compressibility index, Hausner ratio and flow rates. All microspheres presented a narrow particle size distribution and good flow characters according to USP 28-NF 23 criteria, besides microspheres were more spherical in shape in their manufacture with ethylcellulose N100 and higher ratio of both polymers. Thus, in the case of ethylcellulose, the viscosity and ratio of the polymer in dispersion medium were found to be the controlling factors of drug release. Ethylcellulose N10 and N100 membrane materials indicated difference in release patterns of microspheres. Microspheres exhibited lower burst effect with decreased drug release rate, when the drug was incorporated with ethylcellulose N100 and higher ratio of each polymer. Therefore, indomethacin release from ethylcellulose microspheres could not be evaluated by any of the kinetic models.

4. AIM AND OBJECTIVE

Gliclazide is an anti-diabetic drug comes under second generation sulfonylureas, and is a good insulin sensitizer that has been widely used in management of NIDDM. It's half life is 5hours, more than 99% bind to plasma proteins and is absorbed completely from the entire GIT.

Since, Gliclazide is well absorbed from GIT controlled release formulation that retained in the GIT will be beneficial for effectively controlling diabetes. Several methods have been reported which can be used to retain the dosage form in the GIT, which results in the spreading the drug slowly over the absorptive surface in the GIT. A gastro retentive dosage form is one approach that will release the drug over a prolonged period of time in GIT thus enhancing the opportunity for absorption of drug. Considering the above factors, the present work is aimed to formulate and evaluate the Gliclazide microspheres for controlled release in the GIT.

The objective of the present research work would be:-

To develop suitable formula and procedure for the manufacturing of Gliclazide microspheres

- To study the effect of polymer concentrations.
- To evaluate the different parameters of microspheres.
- To perform in vitro drug release study.
- To know the release kinetics.

5. PLAN OF THE WORK

The present work was carried out to design and evaluate the microspheres of gliclazide.

The study is carried out in the following sequences:

1) Preformulation studies
    - Compatibility study using differential scanning calorimetry.
    - Compatibility study using FT-IR spectrophotometry.
2) Preparation of standard curve of gliclazide in pH7.4 buffer .
3) Formulation of gliclazide microspheres Using poloxemer
4) Evaluation of the prepared microspheres of Gliclazide.
    - Particle size.
    - Encapsulation efficiency.
    - Drug content.
    - Percentage yield.
    - Shape and surface characterization of prepared microspheres (SEM).
    - *In-vitro* dissolution studies.
5) Application of drug release kinetics.

6. PROFILES

6.1. DRUG PROFILE [43,44]

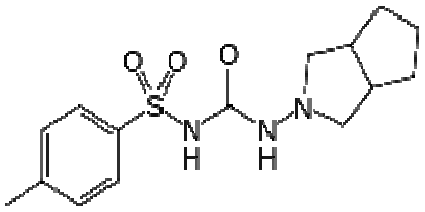
GLICLAZIDE:-

Synonym **:**Gliclazid, gliclazida, gliclazidum.

Category **:**Anti diabetic drug.

Chemical Name **:** Benzenesulfonamide, N- [[(hexahydrocyclopenta[c] pyrrol- 2(1H)-yl)amino]carbonyl]-4-methyl.

Structural formula **:**



Molecular Formula **:** $C_{15}H_{21}N_3O_3S$.

Molecular Weight **:** 323.42

Melting Point : 180-182 ^{0} C

Description **:** Gliclazide is white powder.

Bcs Classification **:** Class II.

Solubility : Gliclazide is freely soluble in dimethyl formamide; slightly soluble in methanol sparingly soluble in methylene chloride; practically insoluble in water. It also dissolves in dilute alkali hydroxides and in dilute acids.

Dose : The usual maintenance dose is 1 to 4 mg, The maximum recommended dose is 8 mg.

PHARMACOKINETICS

Absorption

Completely (100%) absorbed following oral administration. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished.

Distribution

Plasma protein binding is greater than 99%.

Volume of Distribution:

1) Volume of Distribution after oral administration was19.8 to 37.1 L.

2) Volume of Distribution after intravenous administration was 9 L.

Metabolism

Gliclazide undergoes hepatic metabolism. Following either an intravenous or oral dose, gliclazide is completely metabolized by oxidative biotransformation to a major metabolite, cyclohexyl hydroxymethyl derivative (M1), via the hepatic

cytochrome P450 II C9 subsystem. M1 is further metabolized to the carboxyl derivative (M2) by one or several cytosolic enzymes. M1, but not M2, possessed approximately one third of the pharmacologic activity of its parent in an animal model. However, whether the glucose-lowering effect of M1 is clinically significant and is not clear

Excretion

Gliclazide is mainly excreted through kidney. Most of a dose of Gliclazide is excreted in the urine as metabolites (up to 60%). No parent compound is recovered unchanged. About 40% is excreted through Faces.

Gliclazide, clearance increases with decreasing renal function probably due to more unbound drug with hypo albuminemia. The clearance of both metabolites decreased with worsening renal function. Patients with diabetes mellitus and creatinine clearance (CrCL) less than 20 ml/min to more than 50 ml/min were treated with gliclazide 1 to 8 mg/day for 3 months. The dosage was adjusted based on blood glucose response.

Total Body Clearance is 48 to 53 ml/min; and elimination half-life is 5 to 8 hrs after oral administration.

CLINICAL PHARMACOLOGY:-

Mechanism of action

The mechanism of action of Gliclazide in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin. Gliclazide likely binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Membrane depolarization stimulates calcium ion influx through voltage-sensitive calcium channels. This increase intracellular calcium ion concentration induces the secretion of insulin.

PHARMACODYNAMICS

Drug Interactions

Acebutolol :

Acebutolol is Beta blocking agents, administration of this with Gliclazide produce: hypoglycemia, hyperglycemia, or hypertension.

NSAID:

Concomitant use of an NSAID and a sulfonylurea suggest an increased risk of hypoglycemia may occur.

Example: - Aceclofenac, Acemetacin

Over dosage

- After ingestion of an over dosage hypoglycaemia may occur, lasting from 12 to 72 hour, and is accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.
- Nausea, vomiting and epigastric pain may occur.

Contra indications:

Gliclazide is contraindicated in patients with the following conditions:-

- Hypersensitivity to glimepiride, other sulfonylureas or sulfonamides
- Insulin dependent diabetes
- Diabetic coma
- Ketoacidosis
- Pregnancy and lactation
- Severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a changeover to insulin is required.

Adverse effects:

- Asthma
- Blurred vision
- Cholestasis
- Hepatic porphyria
- Hepatitis
- Hyponatremia
- Hypoglycaemia
- Photosensitivity
- Diarrhea, Nausea, Vomiting, and Abdominal pain

Storage **:** It should be stored in dry place at below 25^0C.

Use **:** Used in the treatment of type-II diabetes

6.2 POLYMER PROFILE [45]

POLOXIMER:-

USP **:** POLOXIMER 407

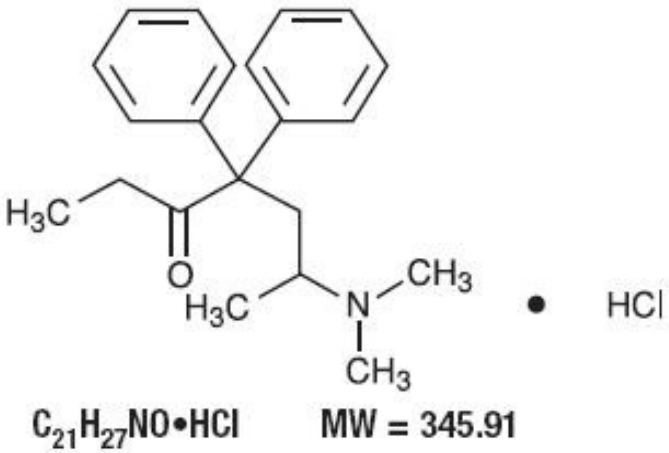
Synonyms : Poloxalkol ;Lutrol ;Monolan; pluronic.

Chemical name **:** α-hydro-ώ-hydroxy poly(oxyethylene) poly(oxypropylene) poly(oxyethylene)

Empirical Formula **:** poloximer polyols are a series of closely related Block copolymers of ethylene oxide and propylene oxide

Molecular weight **:** Molecular weight is approximately (9840-14600 Dalton)

Chemical structure **:**



Functional category : dispersing agent, emulsifying and coemulsifuing agent, solubilizing agent ,tablet lubricant.

Description

color : white color

Physical form : waxy and free flowing prilled granules.

Taste : tasteless

Odour : odorless

Typical properties :-

Density : 1.06 g/ cm3 at25° c

Viscosity : 1000 mPa s (1000cp) as a meltn at a77 °c

Methoxyl Content : 19-24%.

Moisture content : 0.5- 80%.

Melting point : 52-57 c

.**Specific Gravity** : at 25°C : 0.8093 - 0.8157.

Applications

Most of the common uses of poloxamer 407 are related to its surfactant properties. For example, it is widely used in cosmetics for dissolving oily ingredients in water. It can also be found in multi-purpose contact lens cleaning solutions, where its purpose there is to help remove lipid films from the lens. It can also be found in some mouthwashes. There is a research ongoing for using poloxamer 407 for aligning severed blood vessels before gluing them surgically.

Solubility

Poloxamer 407 is a hydrophilic non-ionic surfactant of the more general class of copolymers known as poloxamers. Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol

Stability and storage conditions

Poloxamers are stable matrials. Aqueous solution are stable in a present of acids ,alkalis, metal ions. However, aqueous solutions do support mold growth. The Bulk material should be stored in a well closed container in a cool, dry place.

6.3 EXCIPIENTS PROFILE

6.31 DICHLOROMETHANE

Synonyms : Methane dichloride;

Methylene bichloride;

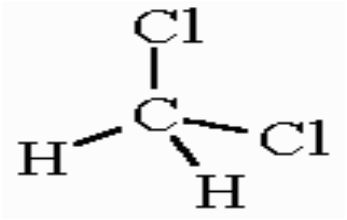
Methylene chloride; Methylene dichloride

Molecular Formula : CH_2Cl_2

Molecular Weight : 84.93

Chemical Name : Dichloromethane

Structural Formula :



Description : Dichloromethane is colorless, volatile liquid with a moderately sweet aroma is widely used as a solvent. Although it is not miscible with water, it is miscible with many organic solvents.

Functional category : Solvent, detergent, vesicant foaming agent.

Density : 1.33 g/cm^3, liquid.

Viscosity : 0.449 mPa's at 15^{0}C, 0.393 mPa's at 30^{0}C.

Boiling Point : 39.8-40.0ºC

Solubility : Slightly soluble (1.38 g/100 mL) in water at 20°C; soluble in carbontetrachloride; miscible in ethanol, Diethyl ether and dimethylformamide

Stability and storage condition : Stable upto 60^0c, it's vapour is nonflammable and is not explosive when mixed with air. But may form explosive mixtures in atmospheres with higher oxygen content.

Applications in pharmaceutical formulation:

Manufacturing of Polycarbonate, Phenolic, Rayon yarn, Solvent for Cellulose Acetates, Photo – resist, Tablet film coatings, Aerosol Propellant, Refrigerant, Adhesives for Polyethylene Methacrylate.

6.3.2. TWEEN 80

Synonyms : Polyoxyethylene (20) sorbitan monooleate

(x)-sorbitan mono-9-octadecenoate poly(oxy-

1,2-ethanediyl) Alkest TW 80;

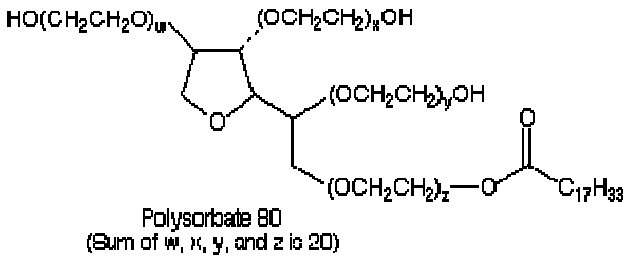
POE (20) sorbitan monooleate

Molecular Formula : $C_{64}H_{124}O_{26}$

Molecular Weight : 428.600006103516

Chemical Name : Tween 80

Structural Formula :



Polysorbate 80
(Sum of w, x, y, and z is 20)

Functional category : Emulsifier, foaming agent, lubricant,

solubilizer, surfactant

Description : Amber-colored viscous liquid. pH (5% aqueous

solution) 5-7.Faint odor and bitter taste

Density : 1.06-1.09 g/ml, oily liquid

Viscosity : 375-480 m.Pa.s at 25^0C.

Boiling point : >100.

Solubility : Easily soluble in cold water, hot water. Soluble in methanol.Soluble in Toluene, alcohol, cottonseed oil, corn oil, Ethyl Acetate. Insoluble in mineral oil.

Stability and storage condition : Keep container tightly closed, cool and well-Ventilated area.Do not store above 32.2°C (90°F). Preferably store at temperature between 50 deg F to 90 deg F.

Applications in pharmaceutical formulation

Polysorbate 80 is an excipient that is used to stabilize aqueous formulations of medications for parenteral administration, and used as an emulsifier in the manufacture of the popular anti-arrhythmic amiodarone. It is also used as an excipient in some European and Canadian influenza vaccines. It is also used in the culture of Mycobacterium tuberculosis in Middle brook 7H9 broth.

7. MATERIALS & INSTRUMENTS

Table-2

7.1. MATERIALS USED

S.NO	INGREDIANTS AND REAGENTS	MANUFACTURER AND SUPPLIER
1	Gliclazide	Mahalakshmi chemicals pvt.ltd hyderabad.
2	Poloximer 407	Signant chemical corp. pvt.ltd, Mumbai.
3	Tween 80	Loba chemie pvt.ltd, Mumbai.
4	Dichloromethane	Medrich Pvt. Ltd
5	Ethanol	Medrich Pvt. Ltd

Table-3

7.2 INSTRUMENTS USED

S.NO	INSTRUMENTS	COMPANY
1	Digital balance	Shimadzu ELB 300,Chennai
2	Probe sonificator	Elektro craft India Pvt.Ltd, Mumbai.
3	Orbitek shaker	Orbitek shaker, chenni.
4	Dissolution apparatus USP XXIII	Veego tablet dissolution apparatus, Mumbai
5	Double beam UV spectrophotometer	Perkin Elmer Lambda-25 UV/VIS spectrometer.
6	FTIR	Perkin Elmer Lambda-25 UV/VIS spectrometer
7	SEM	Shimadzu ELB,Chennai

8. METHODOLOGY

8.1 PREFORMULATION STUDIES

The formulation of any drug substance in to dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of drug substance and provide a frame work for a drug combination with pharmaceutical exciepients in the fabrication of a dosage form.

COMPATIBILITY STUDIES

One of the requirement for the selection of suitable exciepients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FTIR spectrophotometer and Differential scanning calorimeter (DSC) to find out if there is any possible chemical interaction of Gliclazide with poloxamer, ethyl cellulose (EC).

a) Fourier Transform Infrared Spectrophotometer (FTIR) [46]

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy using SHIMADZU- FTIR 410 model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100.The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulation were compared with that of the original spectra.

b) Differential scanning calorimeter (DSC) [47]

Differential scanning calorimeter is used to measure the specific heat and enthalpies of transition. When a sample undergoes a thermal transition, the power to the heater is adjusted to maintain the temperature, and a signed proportional to the power difference is plotted on the second axis of the recorder is known as thermogram. The area under the resulting curve is direct measure of the heat of transition. Thermograms were

obtained by using a differential scanning colorimeter at a heating rate 15^0C/min over a temperature range of 0 to 1000^0C.The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 100 ml/min. For maintain the inert atmospheres.

8.2 CONSTRUCTION OF STANDARD CURVE FOR GLICLAZIDE:

Gliclazide can be estimated spectrophotometrically at 224 nm as it obeys Beer's-Lambert's law limit is the range of 5-25 µg/ml.

Preparation of reagents

Preparation of 7.4 buffer[(48)]

Dissolve 8.5 ml of concentrated HCl in 1000 ml of distilled water.

Preparation of standard drug solution

Stock solution:

100 mg of Gliclazide was dissolved in 100 ml of 7.4 pH, to get a solution of 1000 µg/ml concentration.

Standard solution

10 ml of stock solution was made to 100 ml with 7.4 pH thus giving a concentration of 100 µg/ml. Aliquot of standard drug solution ranging from 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with 7.4 pH. Thus the final concentration ranges from 2-10 µg/ml. Absorbance of each solution was measured at 235 nm against 7.4 pH as a blank. A plot of concentrations of drug versus absorbance was plotted.

The linear regression analysis was done on absorbance data points. A straight line equation was generated to facilitate the calculation of amount of drug.

8.3 Calculation of controlled release dose

Required dose = conventional dose $(1+0.693 \times \tau/t_{1/2})$

Where as, τ = Duration of dose

t = Half life of drug

Required dose = $4 (1+0.693 \times 12/5)$

Required dose = 10mg of Gliclazide.

8.4 PREPARATION OF MICROSPHERES BY EMULSION SOLVENT DIFFUSION EVAPORATION TECHNIQUE [27]

The formulations of different batches of Gliclazide microspheres are given in table 4.

Accurately weighed amount of Gliclazide and poloxamer were dissolved in a mixture of Dichloromethane (DCM): Ethanol (ETN) (1:1) at room temperature. This solution was poured into 100ml distilled water containing 0.1% Tween 80 maintained at a temperature of 30^0-40^0C.The resultant emulsion was stirred with a propeller type agitator at 1200 rpm for 45 mins to allow volatile solvent to evaporate. The resultant microspheres were filtered and dried.

Table-4

Formulation code	Drug:Polymer	Gliclazide (mg)	Poloxamer in (mg)
F1	1:1	10	10
F2	1:2	10	20
F3	1:3	10	30
F4	1:4	10	40
F5	1:5	10	50
F6	1:6	10	60

8.5 EVALUATION OF THE PREPARED MICROSPHERES

8.5.1 Particle size analysis [49]

The particle size of the microsphere is determined by using the optical microscopy method. Microspheres are counted for particle size using a calibrated optical microscope.

8.5.2 Shape and surface characterization [50]

The shape and surface characterization of microspheres are observed under scanning electron microscope(SEM).The microspheres are mounted directly on the SEM sample stub, using double-sided sticking tape, and coated with gold film(thickness 200mm) under reduced pressure (0.001 tort) and photographed.

8.5.3 Determination of drug content [51]

Accurately weighed 10 mg of crushed microspheres were dissolved in PH 7.4 buffer solution and then transferred to 100 ml volumetric flask. The volume was made up to 100mL with 0.1N HCl. The solution was filtered using Whatman filter paper no. 41. The samples were assayed for drug content using UV spectrophotometer at 235 nm.

8.5.4 Determination of percentage yield of microspheres [52]

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below.

$$\text{percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \text{ X100}$$

8.5.5 Encapsulation efficiency [53]

Encapsulation efficiency of microspheres was calculated using the following formula;

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content\%}}{\text{theoretical drug content\%}} \text{ X100}$$

8.5.6 *In-vitro* release studies of drug release [54]

Dissolution parameters

Medium **:** In pH 7.4 buffer solution

Apparatus **:** USP-Type I (basket).

RPM **:** 100

Temperature **:** $37^0 \pm 0.5^0$c

Medium volume **:** 900ml

Sampling Time Interval **:** 1, 2, 3…….12 hours.

Detected by **:** Double beam UV-visible spectrophotometer(nm).

Procedure

In-vitro drug release studies were carried out using the rotating basket method specified in USP XXIII dissolution apparatus (Apparatus I) with 100 rpm speed at 37 ± 0.5^0C. Dissolution was carried out in pH 7.4 buffer solution. The weighed amount of microspheres were wrapped in muslin cloth and kept in baskets. The drug release studies were carried out in 900 ml of pH 7.4 buffer solution as dissolution media. Samples were withdrawn at predetermined time interval (1 h) from each dissolution vessel, filtered using Whatman filter paper; samples were analyzed for drug at 235 nm using a UV visible double beam spectrophotometer.

8.4.8 Kinetics of drug release [55]

In order to understand the mechanism and kinetic of drug release, the drug release data of the in-vitro dissolution study are analysed with various kinetic model like zero order, first order, higuchi's, peppa's and coefficient of correlation (r) values are calculated for the linear curves by regression analysis of the above plots.

Table-5

Mechanism of drug release as per korsemeyer equation/peppa's model

S.No	N Value	Drug release
1.	n < 0.5	Fickian release
2.	0.5<n<1	Non- Fickian release
3.	n>1	Case II transport

9. RESULTS

9.1 COMPATABILITY STUDIES

9.1.1 Fourier Transform Infrared Spectrophotometer (FTIR)

Infrared spectra for pure drug Gliclazide, poloxamer407 vand physical mixture of drug and polymer were determined to check the interaction of drug in the polymer mixture, their spectrums are shown in figures 1 to3.

Figure:1 FTIR SPECTRA OF GLICLAZIDE

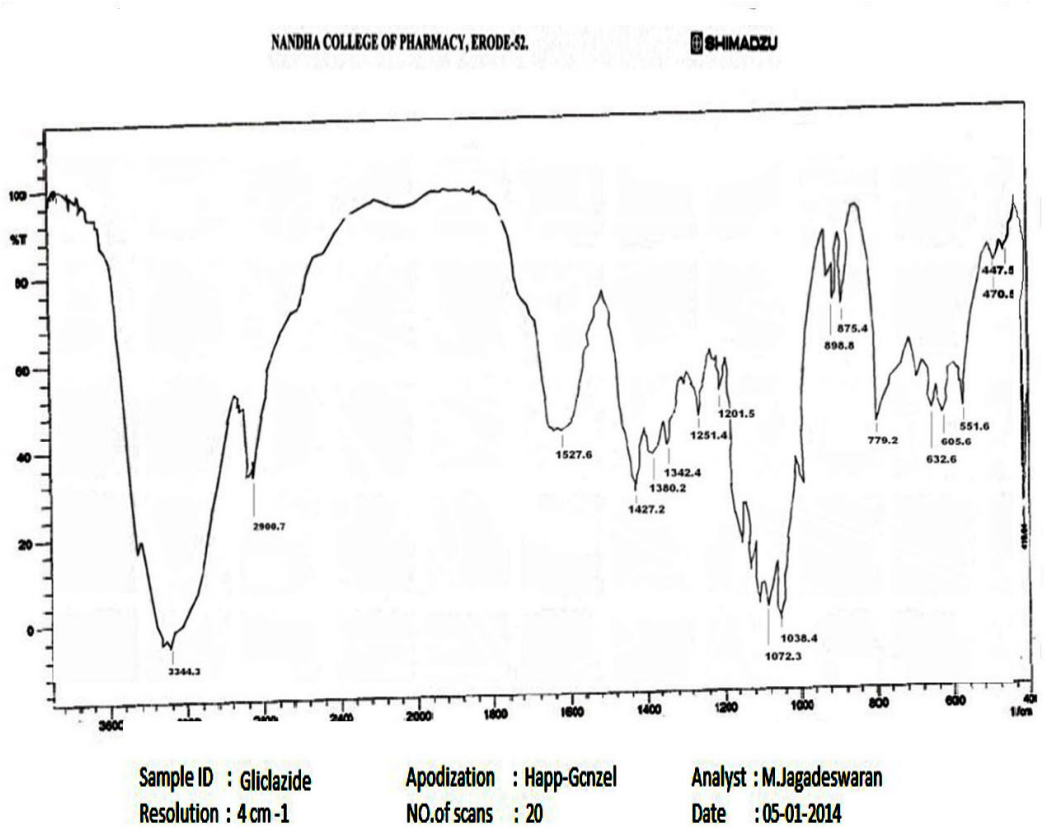


Figure:2 FTIR SPECTRA OF POLOXAMER 407

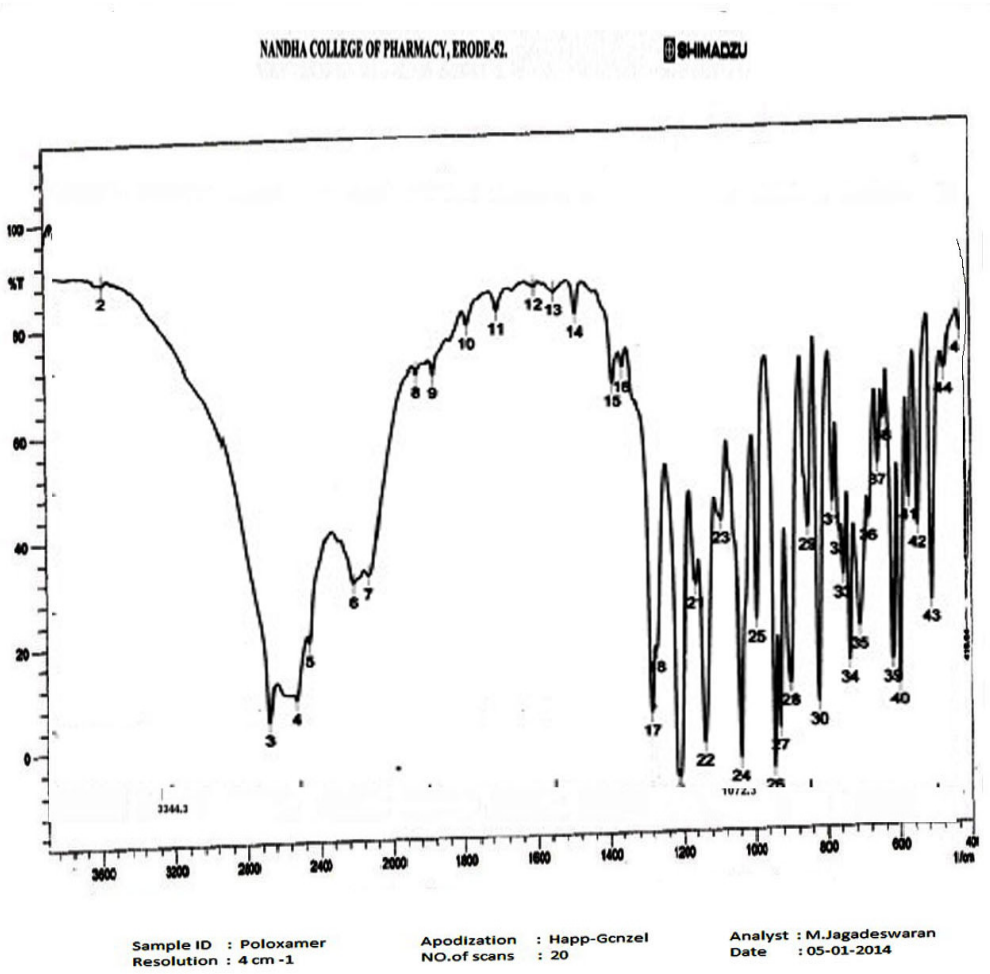
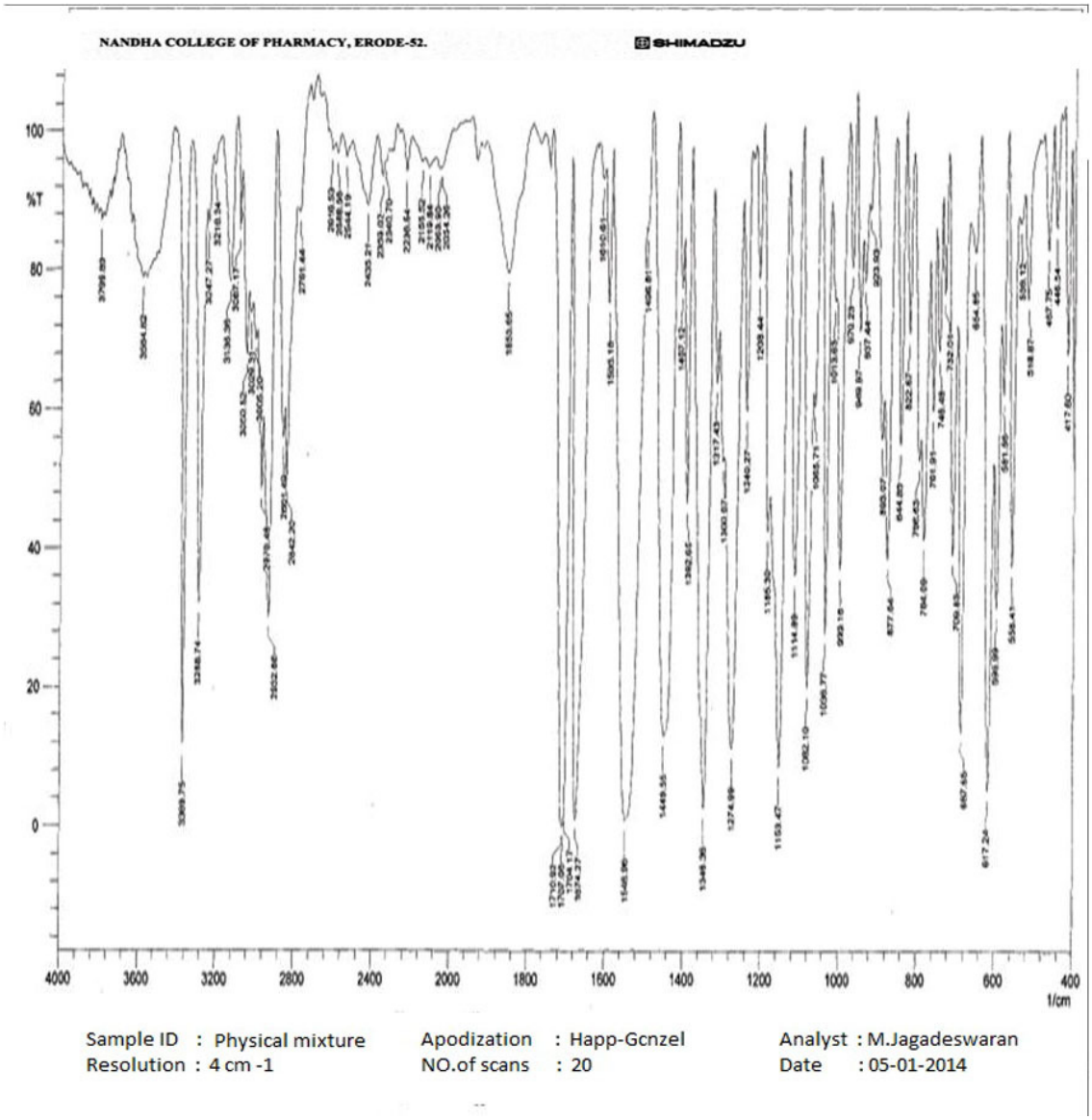


Figure:3 FTIR SPECTRA OF GLICLAZIDE + POLOXAMER 407



9.1.2 Differential scanning calorimeter (DSC)

DSC provides information about physical properties of sample as crystalline or amorphous nature and demonstrates the possible interaction between drug and other polymers.

DSC thermogram of Gliclazide, poloxamer407 and physical mixture of drug and polymers are shown in figures 4-6. Gliclazide showed characteristic endothermic peak at 173.77^{0}C, poloxamer407 showed at 59.76^{0}C.

Figure:4

DSC SPCTRA OF PURE DRUG (GLICLAZIDE)

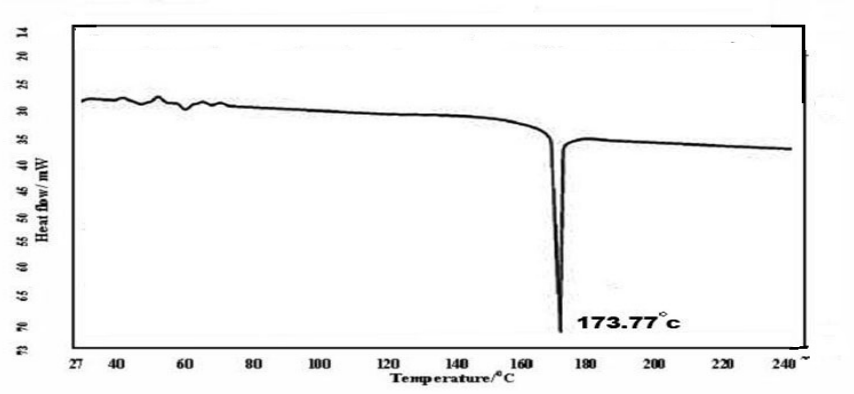


Figure:5

DSC SPCTRA OF POLYMER (POLOXAMER)

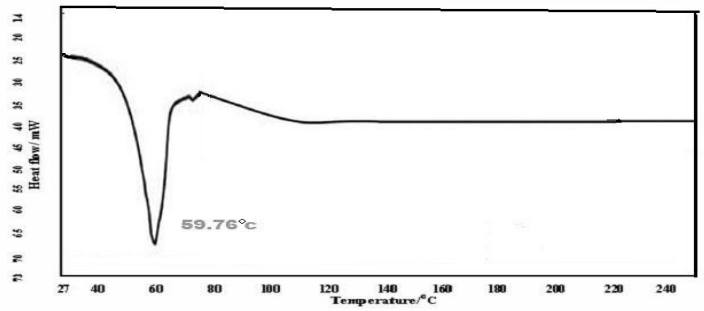
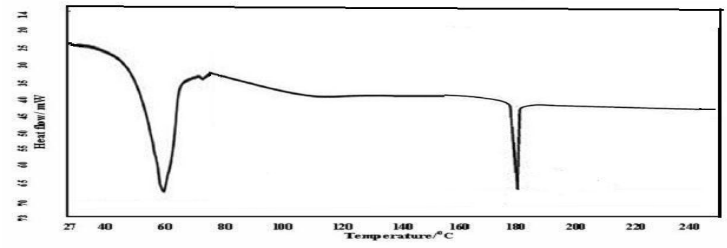


Figure:6

DSC SPCTRA GLICLAZIDE +POLOXAMER



9.2 CONSTRUCTION OF STANDARD CURVE FOR GLICLAZIDE

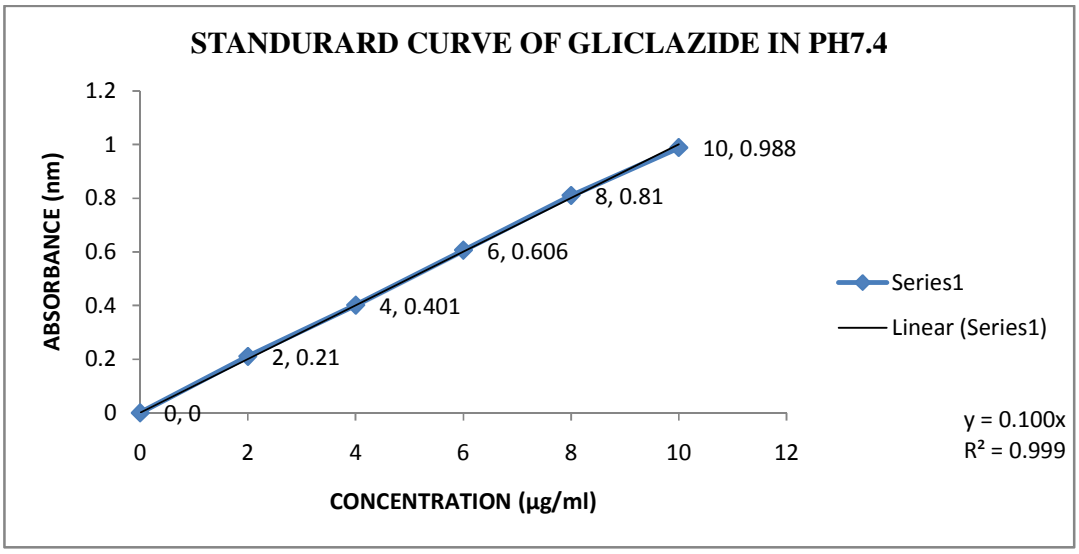
Table:6

Standard curve for Gliclazide

S.NO	Concentration in µg/ml	Absorbance at 235 nm
1	2	0.210
2	4	0.401
3	6	0.606
4	8	0.810
5	10	0.988
Slope		0.100
Correlation coefficient		0.999

Figure:7

STANDARD CURVE FOR GLICLAZIDE IN pH 7.4



9.3 DATA FOR PARTICLE SIZE OF GLICLAZIDE MICROSPHERES (Table:7)

FORMULATION CODE	**MEAN PARTICLE SIZE (µm)**
F1	127±1.563
F1	157±2.039
F3	168±0.935
F4	217±1.178
F5	247±1.825
F6	265±1.509

*Each value represents the mean±S.D. of three experiments

9.4 SHAPE AND SURFACE CHARACTERIZATION OF THE PREPARED GLICLAZIDE MICROSPHERES (SEM)

Scanning electron micrograph (SEM) of the prepared microspheres of Gliclazide is showed in figures 8-10 at different magnifications. SEM images revealed that the microspheres were spherical in shape with a smooth surface morphology.

Scanning electron micrograph (SEM) of the prepared microspheres of Gliclazide formulation

Figure:8

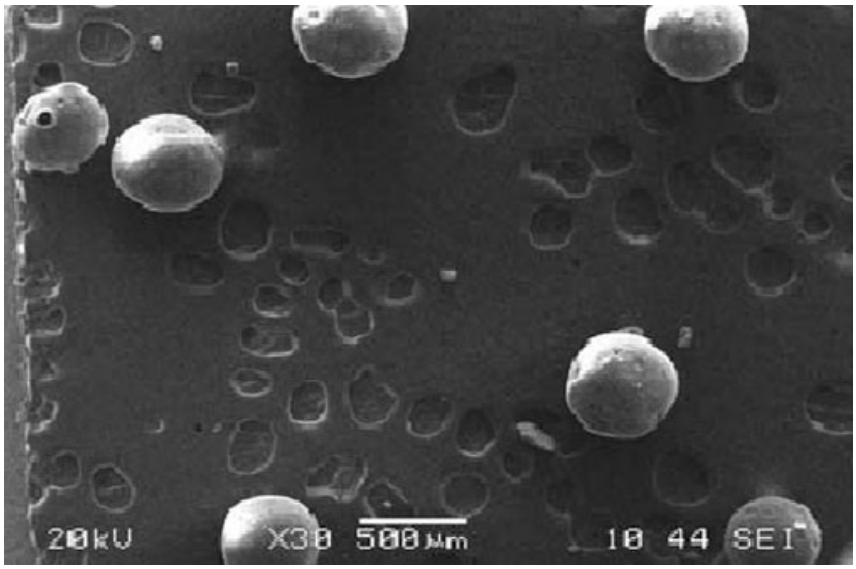


Figure:9

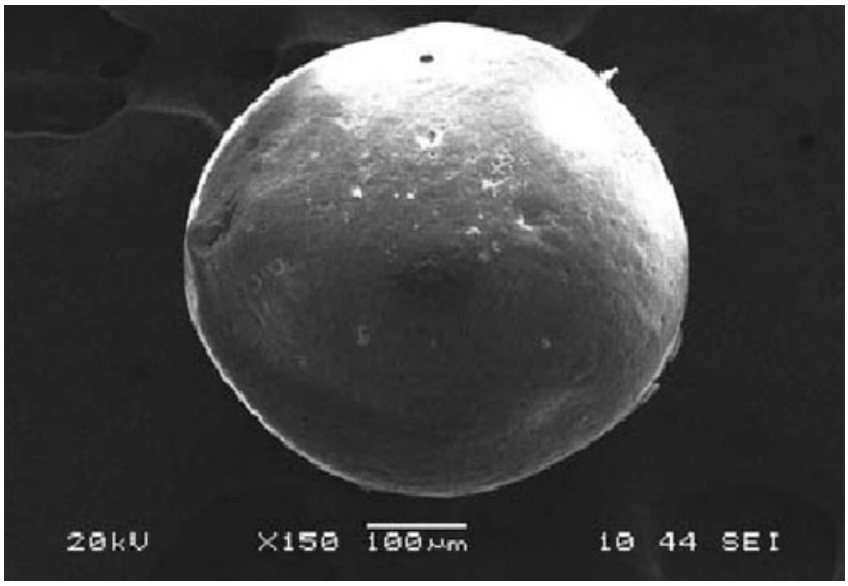
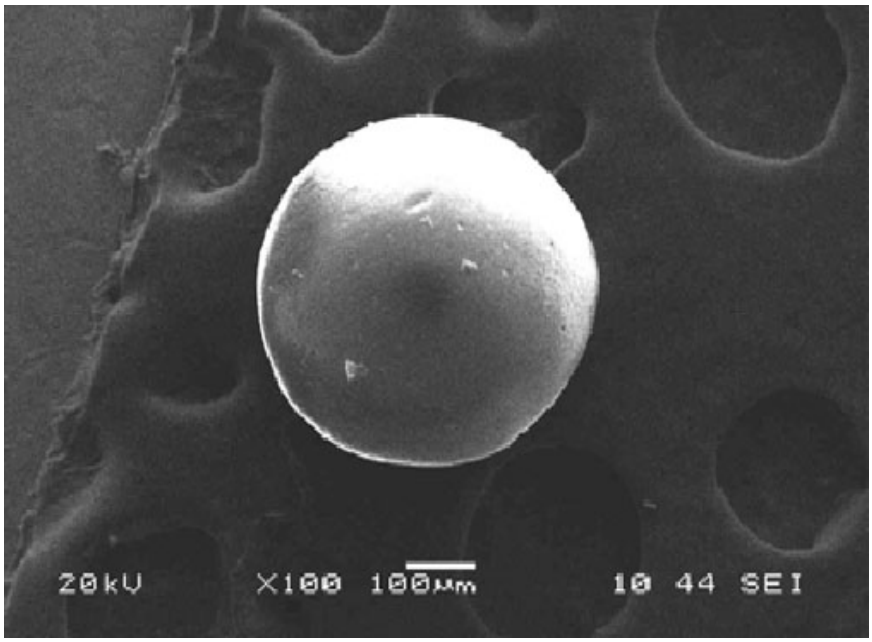


Figure:10



9.5. DATA FOR PERCENTAGE DRUG CONTENT OF GLICLAZIDE MICROSPHERES

Table-8

FORMULATION CODE	PERCENTAGE DRUG CONTENT
F1	70.56±2.274
F2	75.71±0.991
F3	79.21±2.428
F4	84.83±1.541
F5	94.57±1.162
F6	98.16±1.357

*Each value represents the mean±S.D. of three experiments

9.6 DATA FOR PERCENTAGE YIELD OF GLICLAZIDE MICROSPHERES

Table-9

FORMULATION CODE	PERCENTAGE YIELD OF MICROSPHERES
F1	61±1.862
F2	66±1.325
F3	69±1.472
F4	74±2.153
F5	79±1.025
F6	81±1.951

*Each value represents the mean±S.D. of three experiments

9.7. DATA FOR PERCENTAGE DRUG ENTRAPMENT EFFICIENCY OF GLICLAZIDE MICROSPHERES

Table:10

Formulation code	Theoretical drug content in %	Practical drug content in %	Entrapment efficiency in %
F1	6.02	5.38	64.45±2.186
F2	8.15	6.73	72.44±2.38
F3	8.15	6.54	77.14±1.171
F4	9.45	7.29	80.24±1.436
F5	12.92	9.36	82.57±1.325
F6	15.25	9.83	89.36±2.428

9.8 DATA FOR INVITRO DRUG RELEASE OF GLICLAZIDE MICROSPHERES:-

Table: 11

***In Vitro* Drug release of Formulation F1**

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.009	0.232	2.094	10.47±2.145
2	0.012	0.308	2.78	13.92±0.978
3	0.017	0.435	3.92	19.63±1.689
4	0.021	0.537	4.84	24.20±2.146
5	0.024	0.624	5.62	28.14±1.507
6	0.031	0.795	7.16	35.81±1.307
7	0.037	0.936	8.43	42.16±1.624
8	0.042	1.073	9.66	48.33±1.364
9	0.048	1.209	10.88	54.42±1.759
10	0.052	1.323	11.91	59.56±1.158
11	0.056	1.408	12.67	63.39±2.076
12	0.058	1.472	13.25	66.25±1.379

*Each value represents the mean±S.D. of three experiments

Figure:11

***IN-VITRO* DRUG RELEASE PLOT FOR F1**

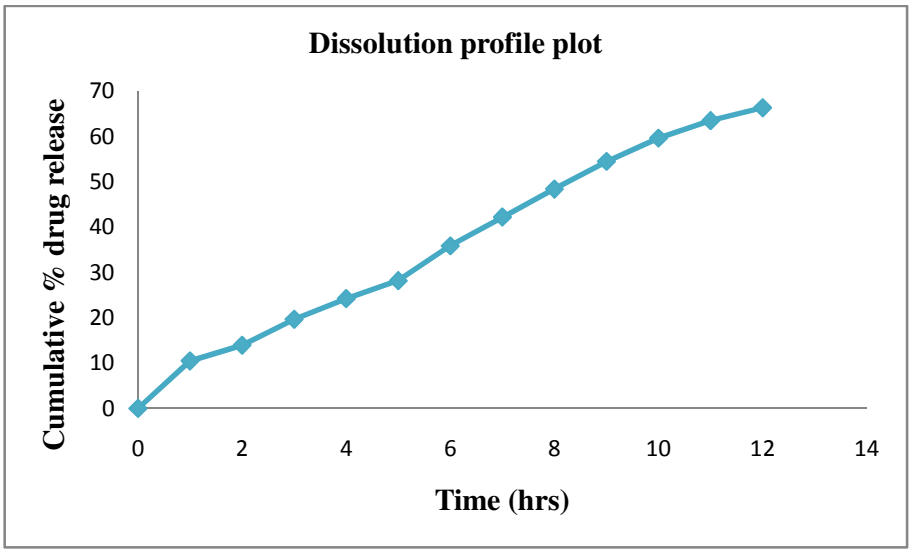


Figure:12

KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F1

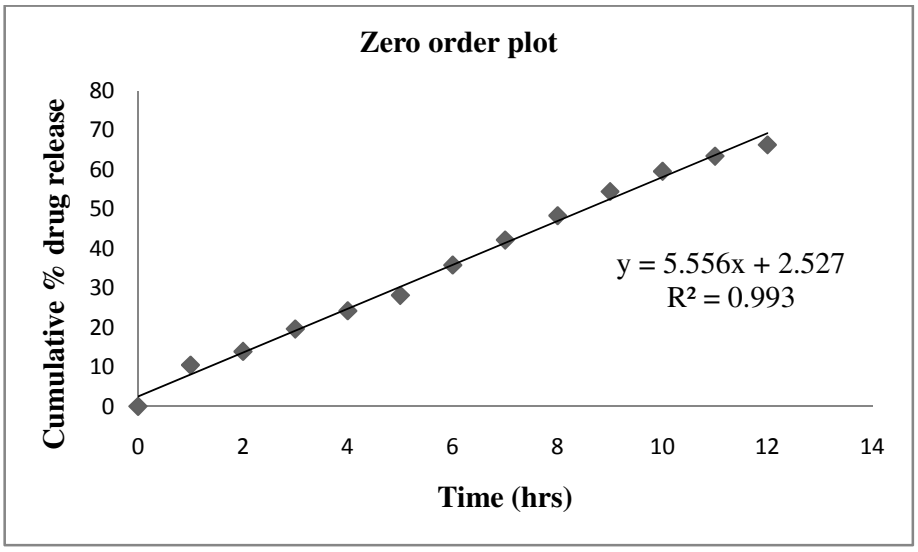


Figure:13

KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F1

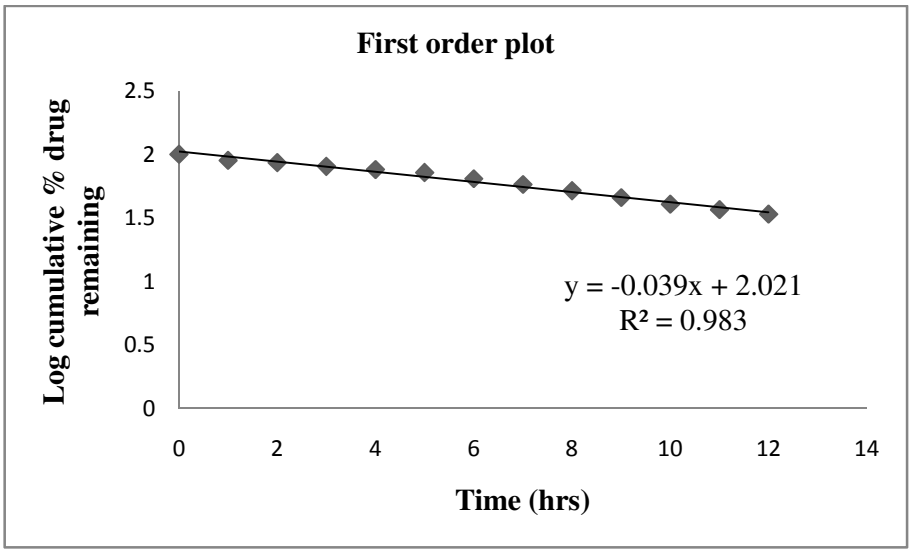


Figure: 14

KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F1

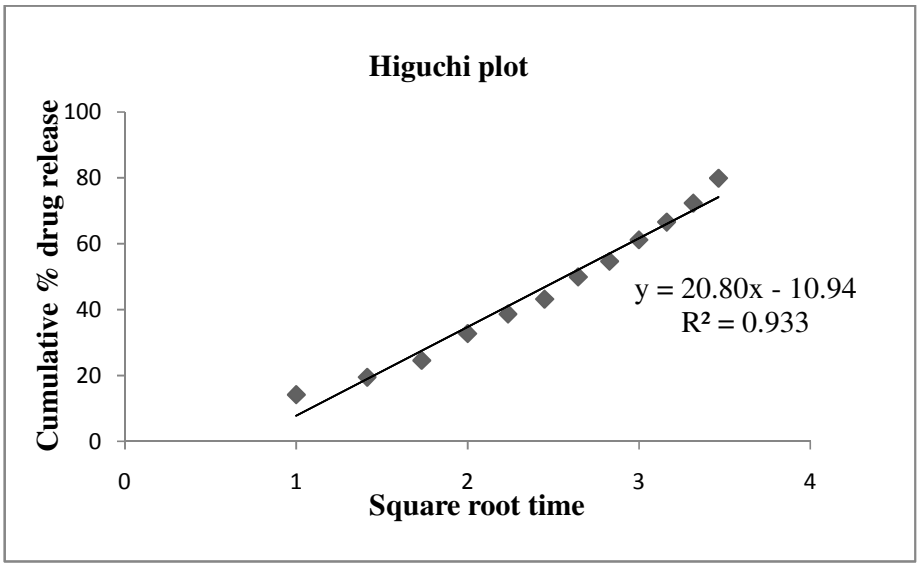


Figure: 15

KINETIC PLOT OF KORESMEYER – PEPPA'S DRUG RELEASE FOR F1

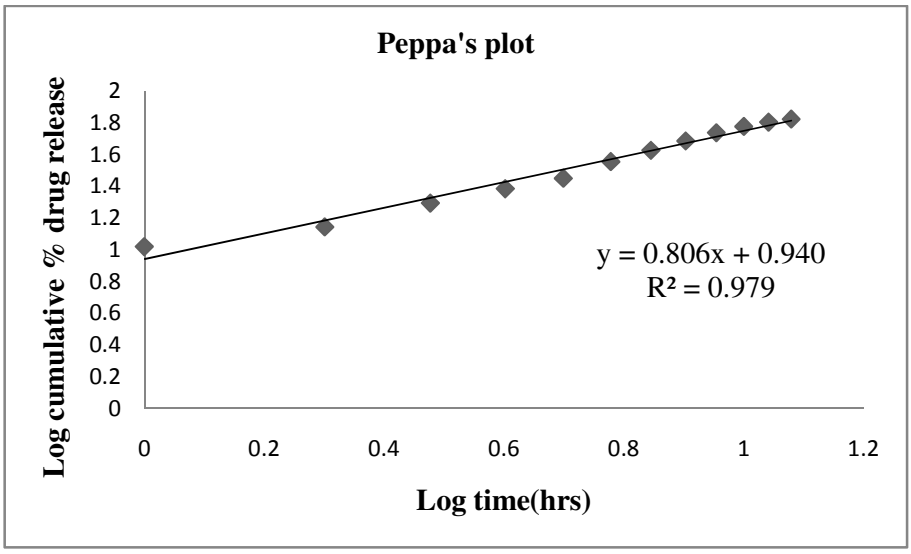


Table:12

***In -Vitro* Drug release of Formulation F2**

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.014	0.36	3.24	16.21±1.406
2	0.018	0.47	4.28	21.42±1.819
3	0.022	0.56	5.06	25.32±1.462
4	0.028	0.70	6.36	31.82±1.879
5	0.032	0.82	7.44	37.21±1.094
6	0.038	0.97	8.76	43.81±1.249
7	0.042	1.07	9.65	48.27±1.657
8	0.048	1.2	10.86	54.31±1.953
9	0.054	1.37	12.37	61.88±2.543
10	0.059	1.49	13.44	67.21±1.527
11	0.063	1.59	14.31	71.58±1.249
12	0.065	1.64	14.76	73.82±1.315

*Each value represents the mean±S.D. of three experiments

Figure: 16

***IN-VITRO* DRUG RELEASE PLOT FOR F2**

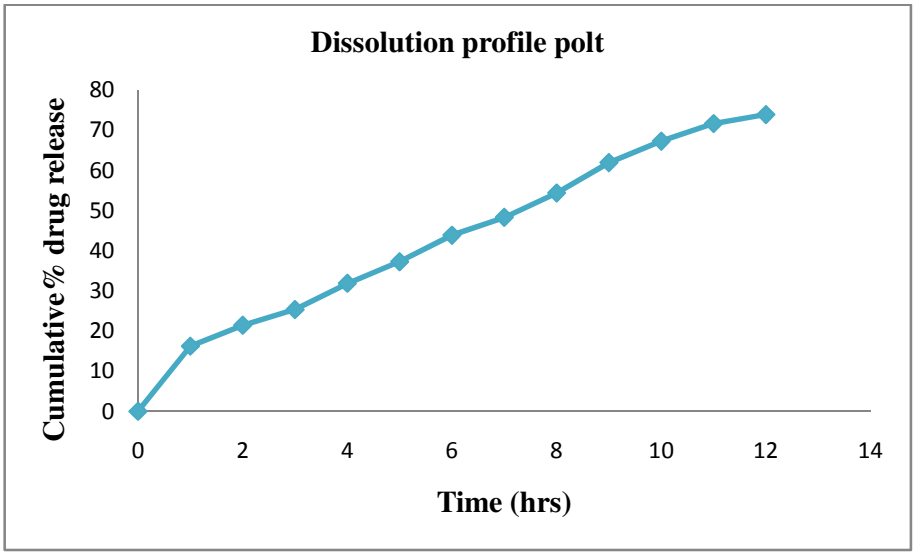


Figure:17

KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F2

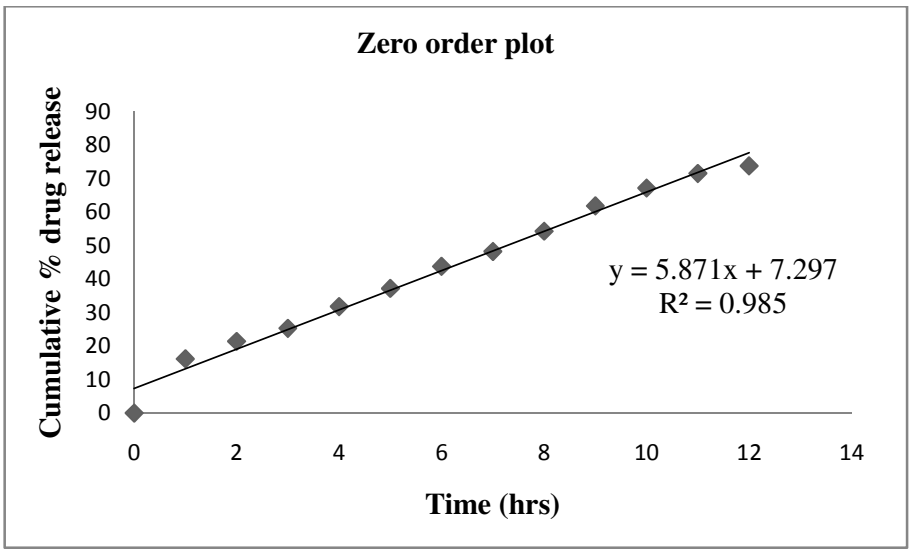


Figure: 18

KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F2

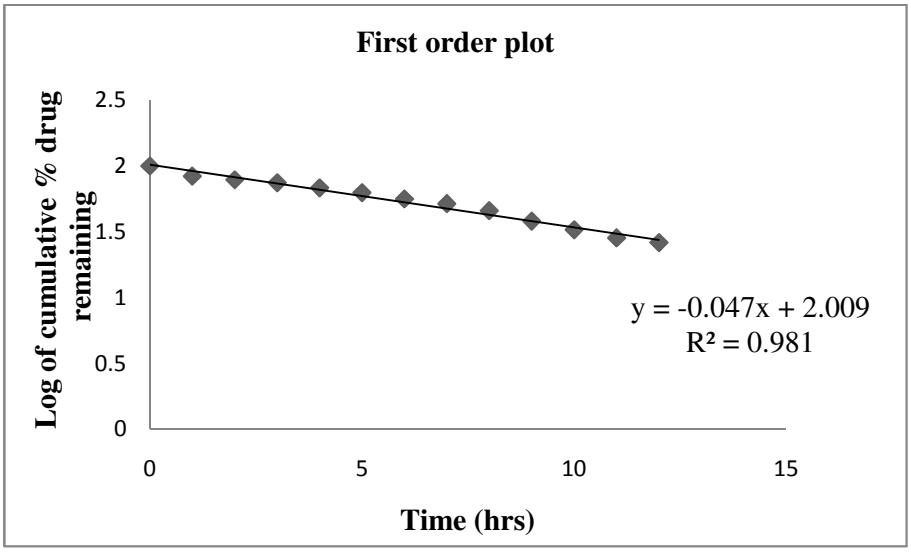


Figure: 19

KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F2

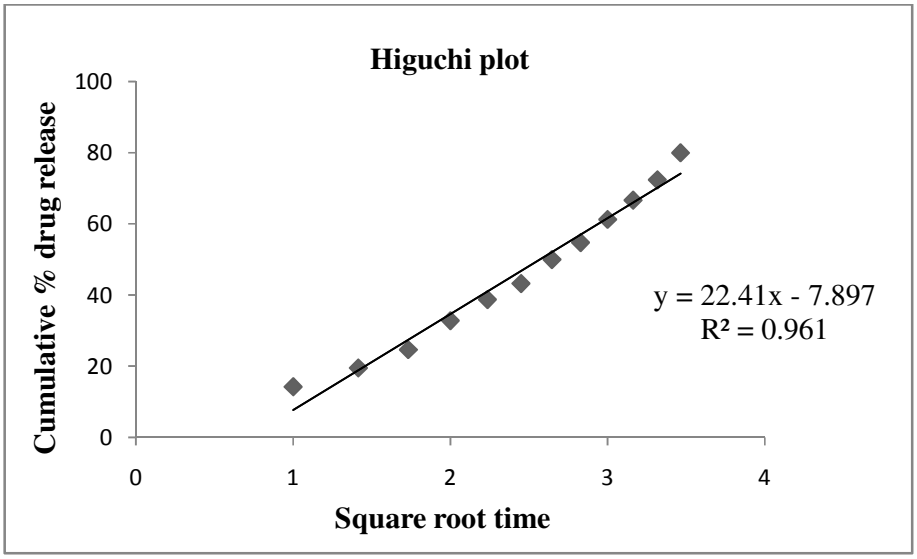


Figure: 20

KINETIC PLOT OF KORESMEYER - PEPPA'S DRUG RELEASE FOR F2

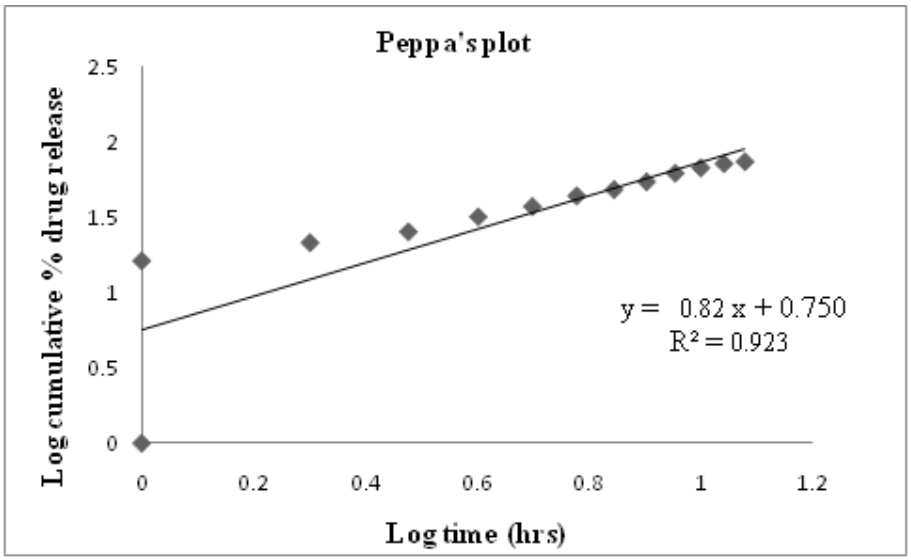


Table :13

***In- Vitro* Drug release of Formulation F3**

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.011	0.294	2.65	13.25±0.185
2	0.014	0.370	3.33	16.67±1.209
3	0.018	0.474	4.27	21.36±1.115
4	0.021	0.548	4.93	24.68±1.462
5	0.025	0.626	5.63	28.18±1.325
6	0.030	0.764	6.88	34.41±1.415
7	0.036	0.919	8.27	41.37±1.981
8	0.042	1.056	9.50	47.54±1.359
9	0.048	1.218	10.96	54.83±1.628
10	0.055	1.394	12.54	62.74±1.537
11	0.061	1.536	13.82	69.14±1.645
12	0.068	1.708	15.37	76.87±1.963

*Each value represents the mean±S.D. of three experiments

Figure: 21

***IN-VITRO* DRUG RELEASE PLOT FOR F3**

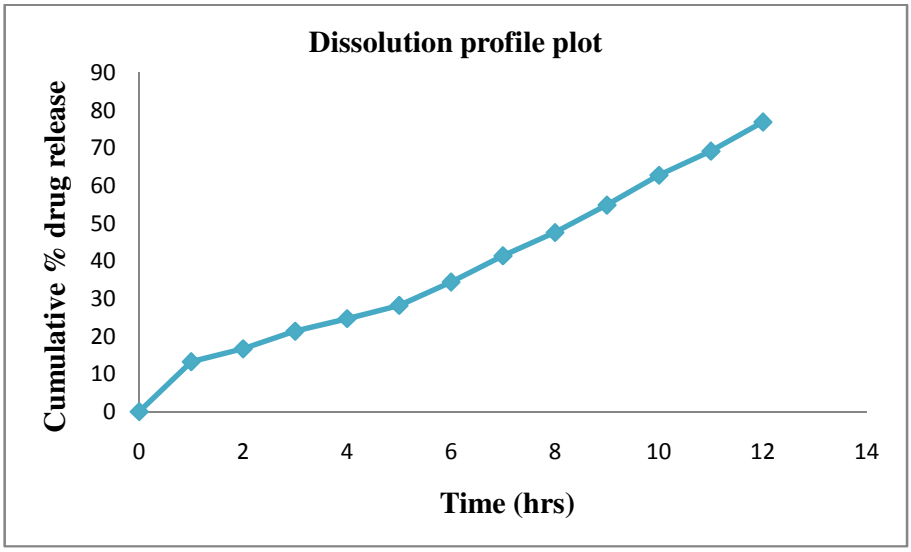


Figure: 22

KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F3

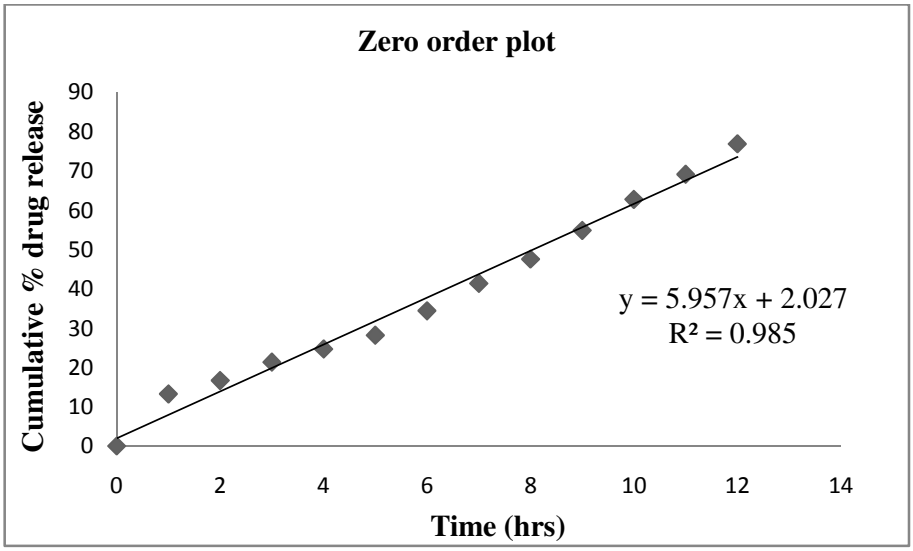


Figure: 23

KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F3

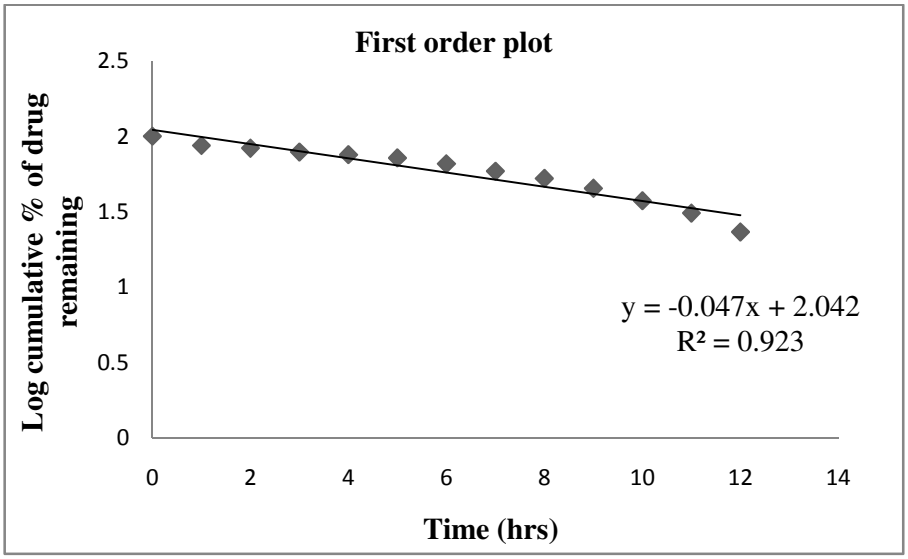


Figure: 24

KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F3

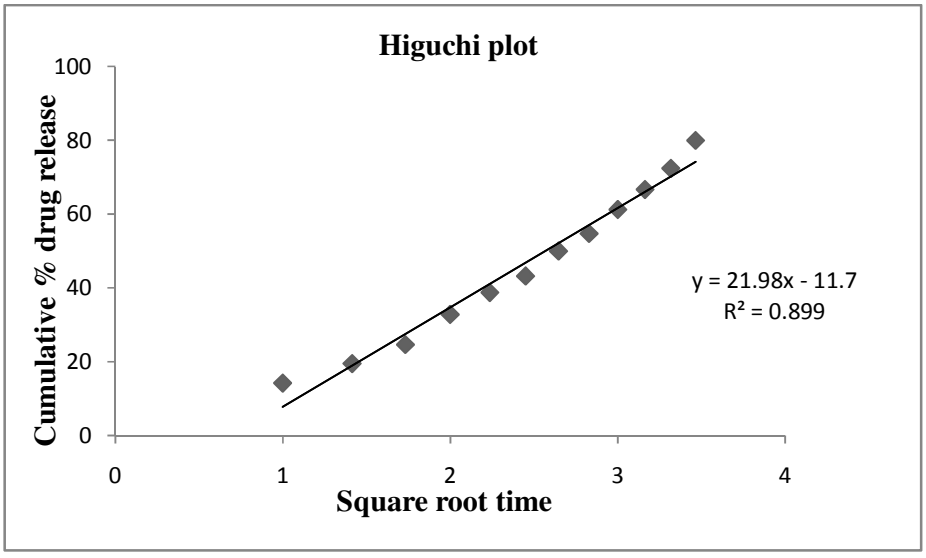


Figure: 25

KINETIC PLOT OF KORESMEYER - PEPPA'S DRUG RELEASE FOR F3

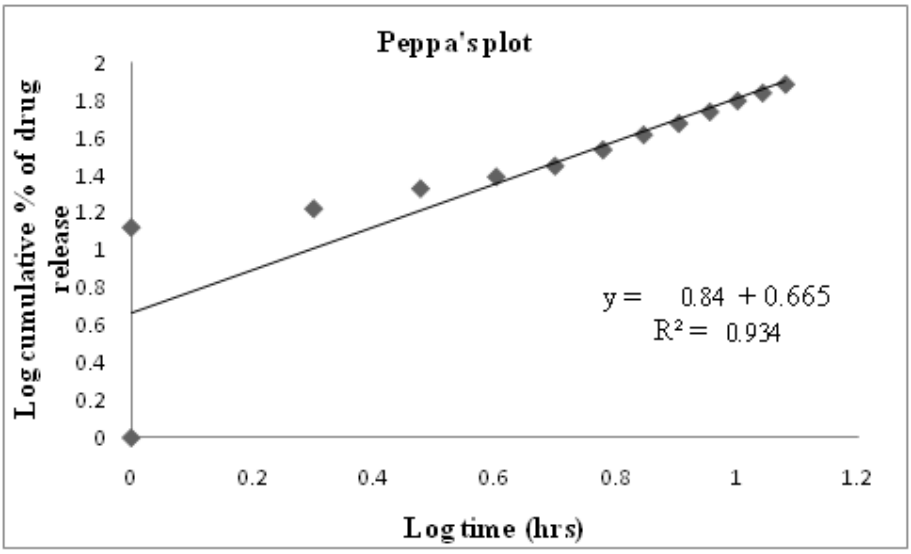


Table: 14

***In- Vitro* Drug release of Formulation F4**

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.0126	0.315	2.84	14.21±1.691
2	0.0173	0.433	3.9	19.50±1.052
3	0.021	0.547	4.92	24.63 ± 1.527
4	0.029	0.728	6.56	32.8±1.694
5	0.034	0.86	7.74	38.73±1.653
6	0.038	0.96	8.64	43.21±1.951
7	0.044	1.11	9.99	49.98±1.668
8	0.048	1.21	10.94	54.72±1.364
9	0.054	1.36	12.24	61.24±1.495
10	0.059	1.481	13.33	66.65±1.724
11	0.064	1.608	14.47	72.37±1.082
12	0.071	1.776	15.99	79.96±1.619

*Each value represents the mean±S.D. of three experiments

Figure:26

***IN-VITRO* DRUG RELEASE PLOT FOR F4**

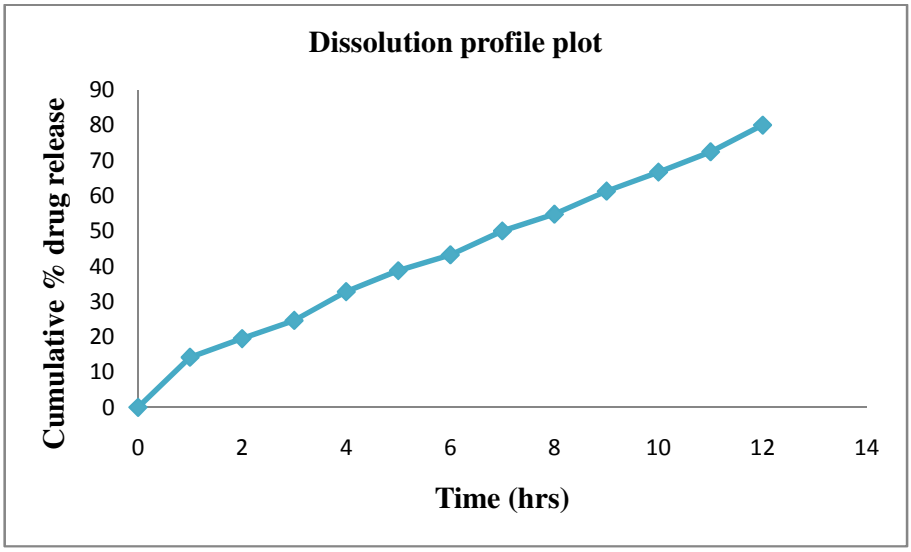


Figure:27

KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F4

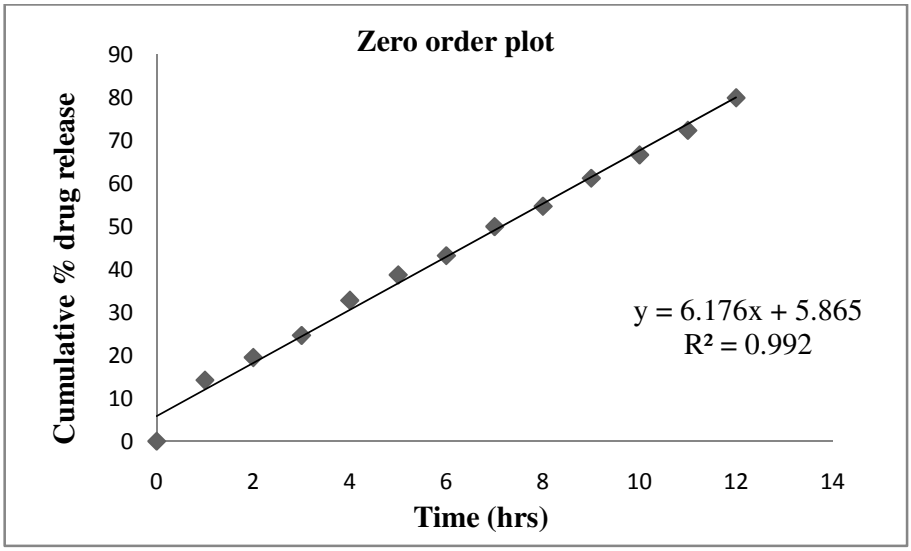


Figure:28

KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F4

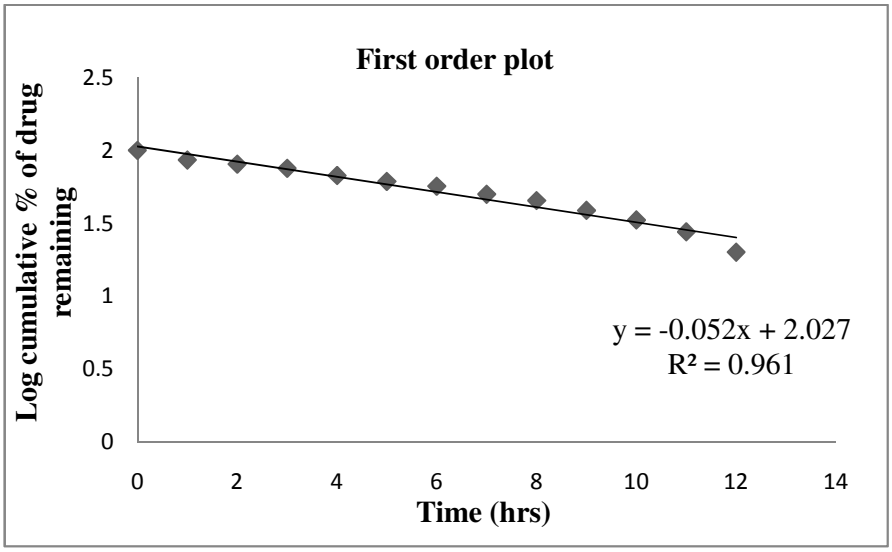


Figure:29

KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F4

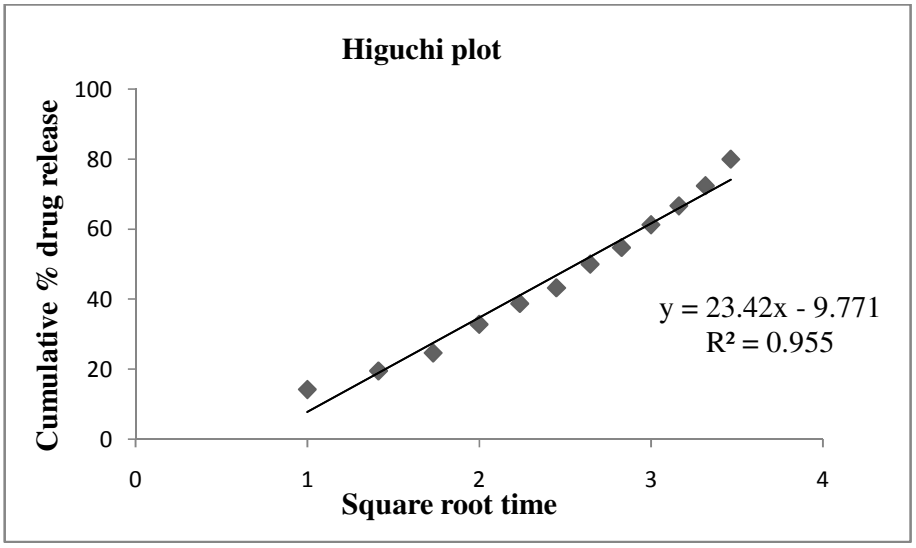


Figure:30

KINETIC PLOT OF KORESMEYER - PEPPA'S DRUG RELEASE FOR F4

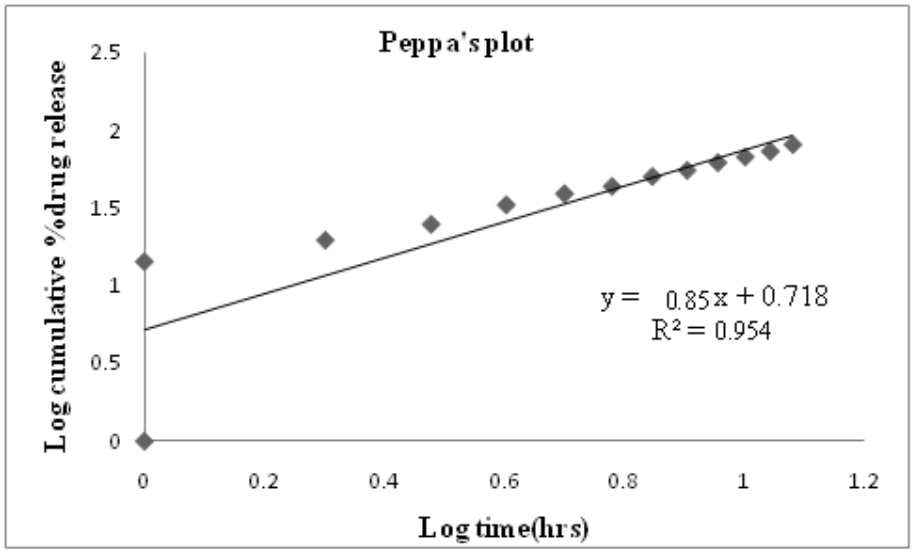


Table-15

***In Vitro* Drug release of Formulation F5**

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.014	0.352	3.17	15.87±1.524
2	0.016	0.406	3.65	18.27±1.432
3	0.024	0.62	5.58	27.90±1.586
4	0.028	0.724	6.52	38.85±2.054
5	0.034	0.863	7.77	43.17±2.364
6	0.038	0.959	8.63	
7	0.045	1.142	10.27	51.39±1.561
8	0.053	1.342	12.08	60.42±1.429
9	0.060	1.516	13.65	68.25±1.357
10	0.066	1.661	14.95	74.76±1.438
11	0.071	1.790	16.11	80.56±1.215
12	0.075	1.882	16.94	84.73±1.365

*Each value represents the mean±S.D. of three experiments

Figure: 31

***IN-VITRO* DRUG RELEASE PLOT FOR F5**

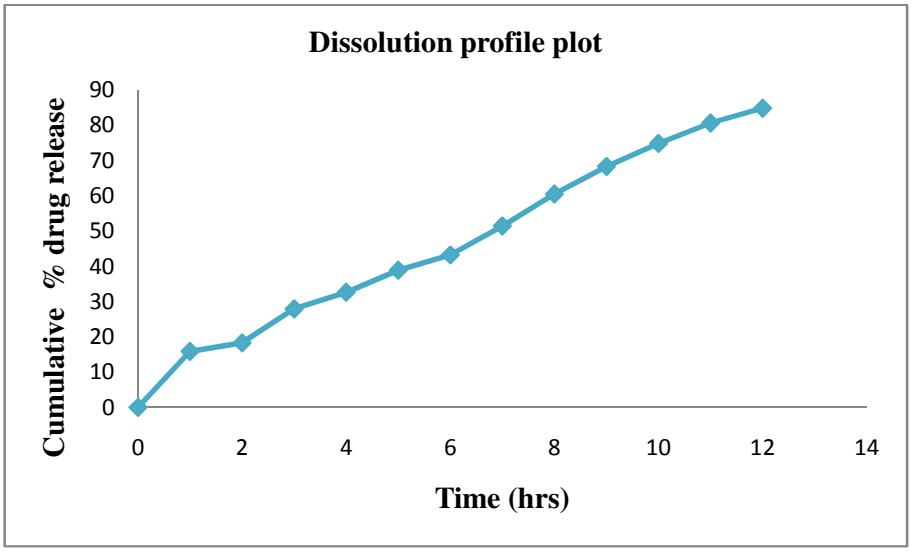


Figure: 32

KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F5

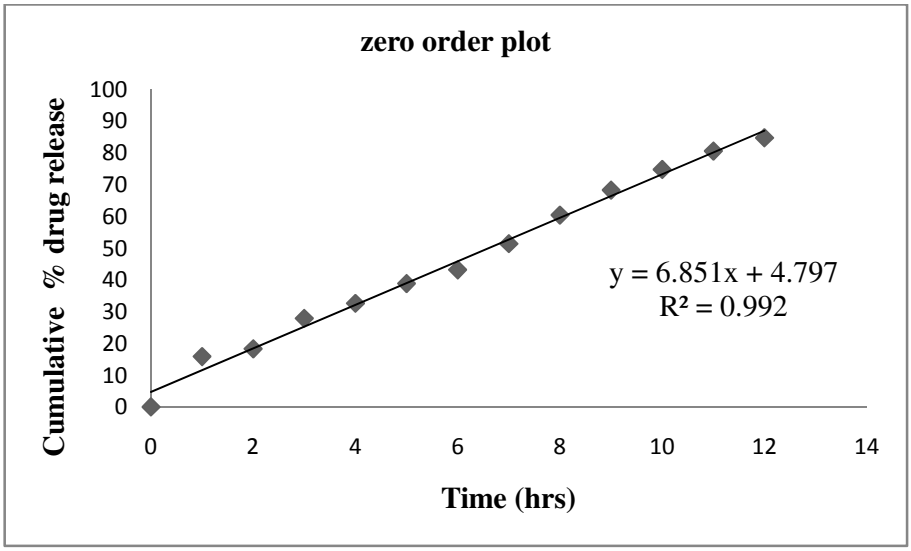


Figure: 33

KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F5

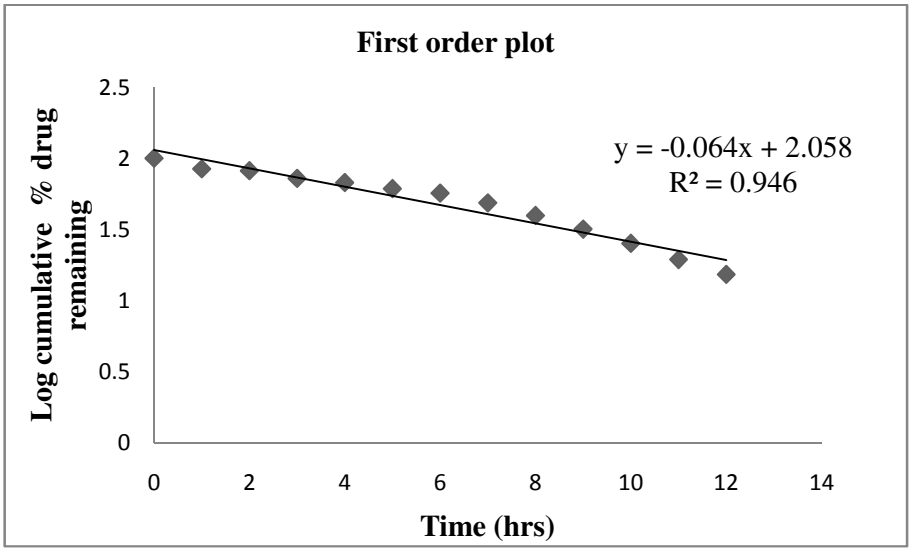


Figure: 34

KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F5

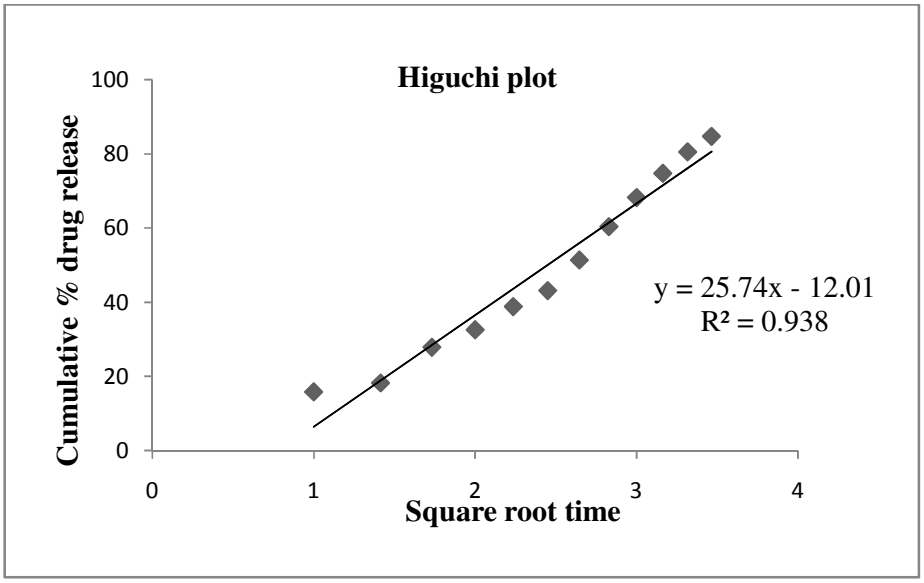


Figure : 35

KINETIC PLOT OF KORESMEYER - PEPPA'S DRUG RELEASE FOR F5

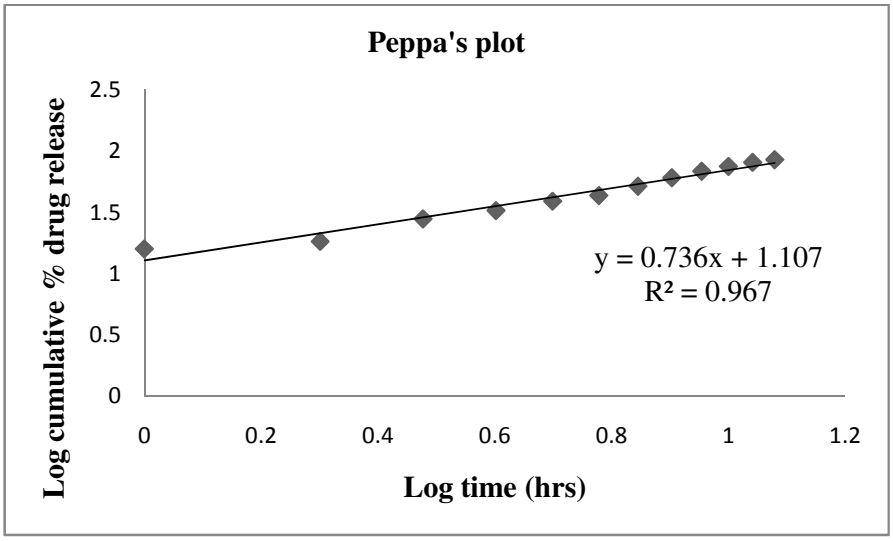


Table-16

***In- Vitro* Drug release of Formulation F6**

Time (hrs)	Absorbance (nm)	Concentration µg/ml	Amount of drug release	Cum % of drug release
0	0	0	0	0
1	0.0154	0.387	3.484	17.42±0.975
2	0.023	0.576	5.186	25.93±2.401
3	0.0316	0.790	7.118	35.59±1.246
4	0.042	1.05	9.492	47.46±1.652
5	0.05	1.257	11.316	56.58±1.752
6	0.053	1.33	12.044	60.22±1.462
7	0.060	1.503	13.528	67.64±1.325
8	0.066	1.67	15.054	75.27±1.425
9	0.073	1.826	16.438	82.19±1.546
10	0.077	1.940	17.466	87.33±1.159
11	0.081	2.031	18.286	91.43±1.879
12	0.083	2.085	18.77	93.85±1.042

*Each value represents the mean±S.D. of three experiments

Figure: 36

***IN-VITRO* DRUG RELEASE PLOT FOR F6**

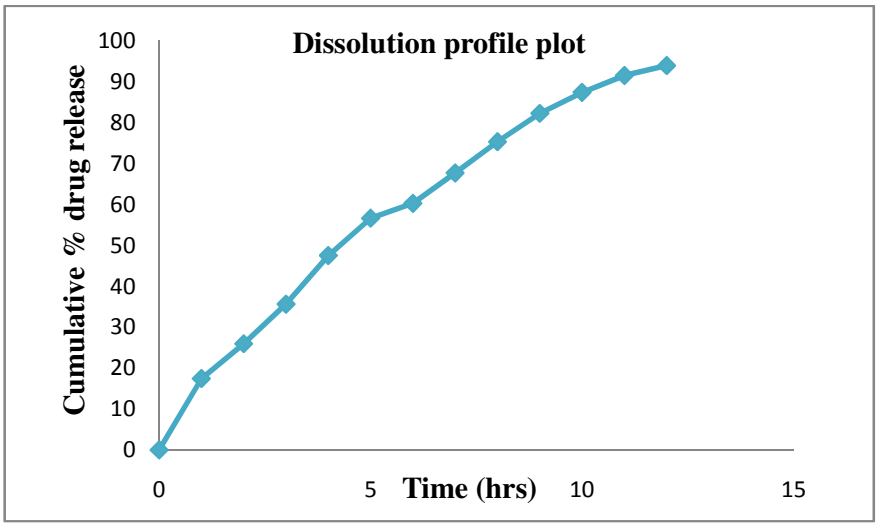


Figure: 37

KINETIC PLOT OF ZERO ORDER DRUG RELEASE FOR F6

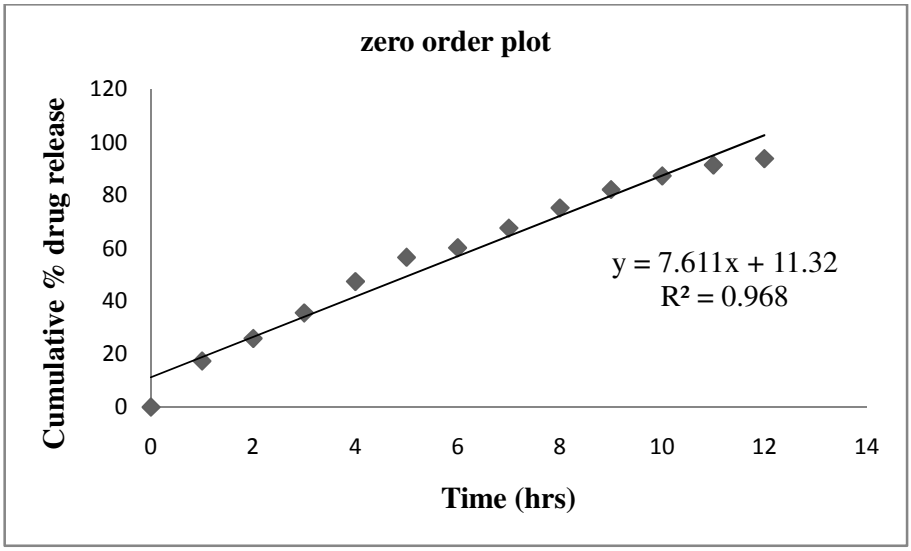


Figure: 38

KINETIC PLOT OF FIRST ORDER DRUG RELEASE FOR F6

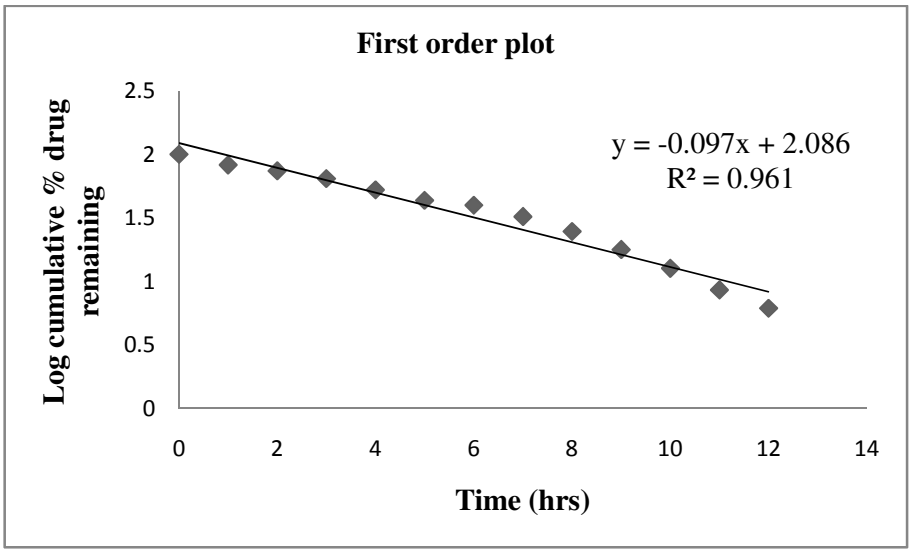


Figure: 39

KINETIC PLOT OF HIGUCHI DRUG RELEASE FOR F6

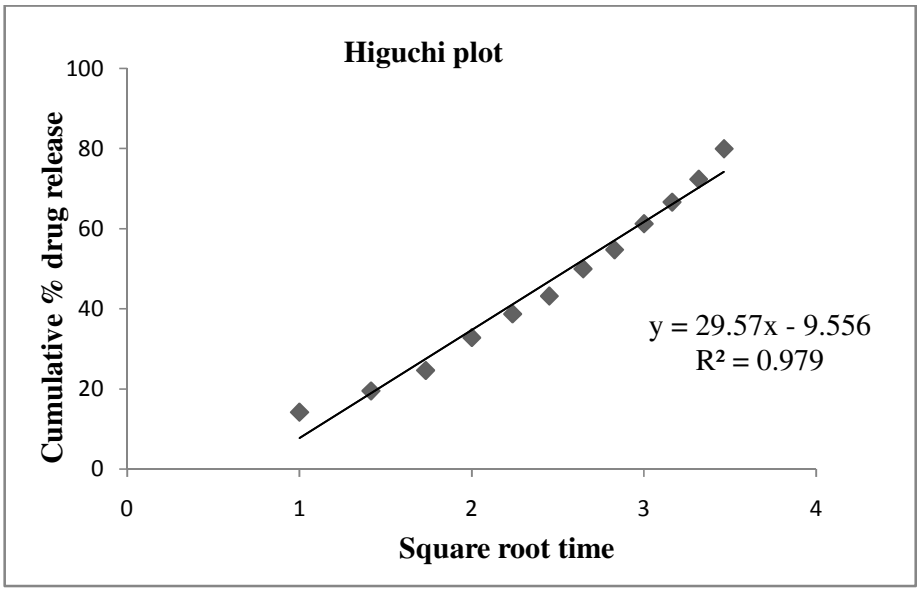
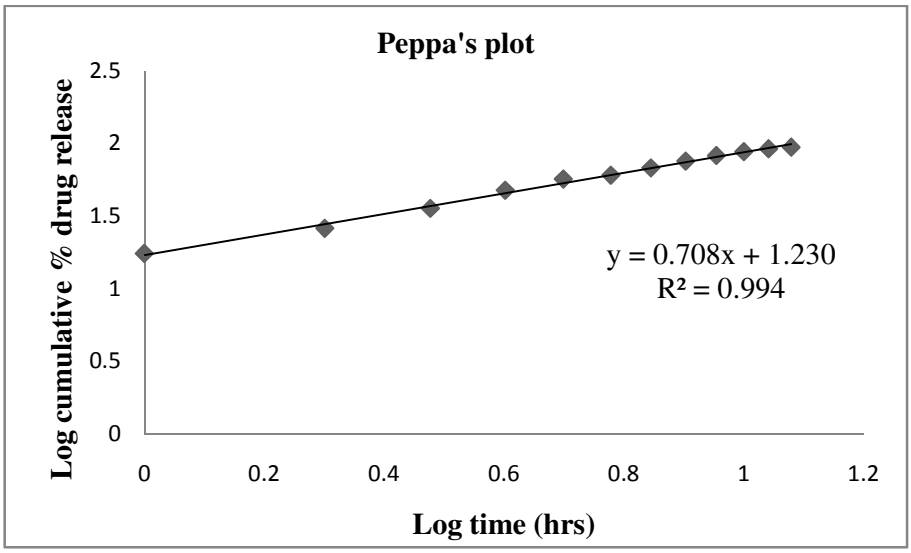


Figure: 40

KINETIC PLOT OF KORESMEYER - PEPPA'S DRUG RELEASE FOR F6



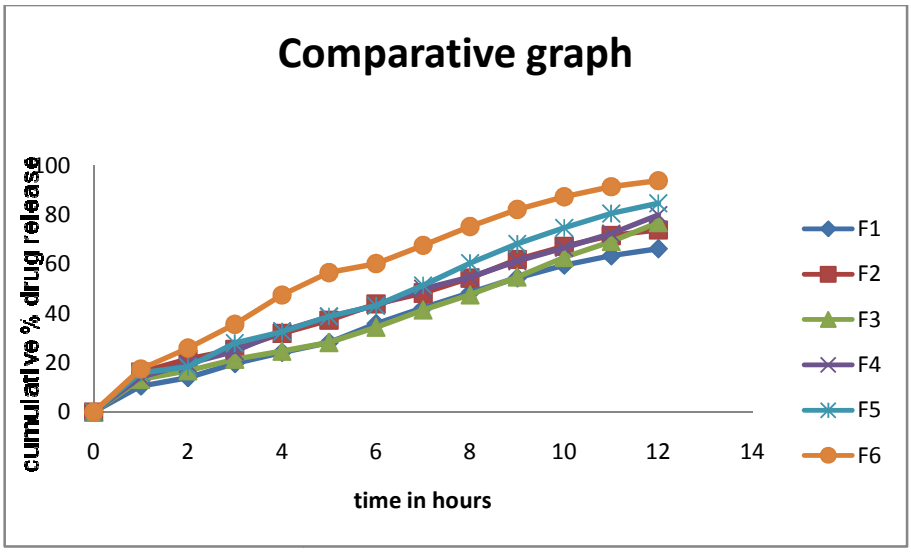
DATA FOR *IN-VITRO* CUMULATIVE PERCENTAGE DRUG RELEASE OF F1 TO F6 FORMULATIONS

TABLE:17

TIME in Hrs	**FORMULATION CODE AND CUMULATIVE PERCENTAGE OF DRUG RELEASE**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	10.47	16.21	13.25	14.21	15.87	17.42
2	13.92	21.42	16.67	19.50	18.27	25.93
3	19.63	25.32	21.36	24.63	27.90	35.59
4	24.20	31.82	24.68	32.8	32.62	47.46
5	28.14	37.21	28.18	38.73	38.85	56.58
6	35.81	43.81	34.41	43.21	43.17	60.22
7	42.16	48.27	41.37	49.98	51.39	67.64
8	48.33	54.31	47.54	54.72	60.42	75.27
9	54.42	61.88	54.83	61.24	68.25	82.19
10	59.56	67.21	62.74	66.65	74.76	87.33
11	63.39	71.58	69.14	72.37	80.56	91.43
12	66.25	73.82	76.87	79.96	84.73	93.85

FOR COMPARATIVE *IN-VITRO* CUMULATIVE PERCENTAGE DRUG RELEASE OF F1 TO F6 FORMULATIONS

Figure: 41



IN-VITRO KINETIC DATA OF F1 TO F6 FORMULATIONS

Table-18

Formula Code	Zero-order Plots	First- order Plots	Higuchi's Plots	Koresmeyer-Peppa's plot		Possible Drug Release mechanism
	Regression Coefficients (R^2)	Regression Coefficients (R^2)	Regression Coefficients (R^2)	Slope (n)	Regression Coefficients (R^2)	
F1	0.993	0.983	0.933	0.806	0.909	Zero-order Non-Fickian release
F2	0.985	0.981	0.961	0.82	0.923	Zero-order Non-Fickian release
F3	0.985	0.923	0.899	0.84	0.934	Zero-order Non-Fickian release
F4	0.992	0.961	0.955	0.85	0.957	Zero-order Non-Fickian release
F5	0.992	0.946	0.938	0.736	0.967	Zero-order Non-Fickian release
F6	0.968	0.961	0.979	0.708	0.934	Zero-order Non-Fickian release

10. DISCUSSION

Gliclazide is an anti-diabetic drug comes under the category of second-generation sulfonylurea and is very potent drug. It acts as insulin sensitizer that has been widely used in management of NIDDM. Its half life is 5 hrs and more than 99% bind to plasma proteins. It is absorbed from entire GIT and is mainly excreted through urine remaining through feces. Gliclazide should be administered with breakfast or the first main meal. and recommended dose is minimum 20mg to maximum 80mg per day.

In the present work efforts have been made to develop microspheres for controlled drug delivery of gliclazide by emulsion solvent diffusion-evaporation technique using various proportions of poloximer 407 as a polymer.

Polymer concentration is the major factor for controlling the drug release. Poloxamer 407 formulations led to enhanced solubilisation of poorly water-soluble drugs and prolonged release profile for many galenic applications (e.g., oral, rectal, topical, ophthalmic, nasal and inject able preparations). Poloxamer 407 formulations having the dissolution follow a zero-order kinetics due to the rapid dissolution of Poloxamer 407 in the receptor fluid and present advantages of promoting stabilization and water dissolution of many pharmacological drugs. New trends suggest combining Poloxamer 407 with other copolymers (e.g., thickening agents, other types of poloxamers). [63]

The FTIR and DSC spectral analysis showed that there was no appearance or disappearance of any characteristic peak of pure drug, physical mixture of drug and polymer, which confirms the absence of chemical interaction between the drug and polymer.

Microspheres were prepared using a gradually increasing polymer concentration in combination with a fixed dose concentration of the drug to assess the effect of polymer concentration on the size of the microspheres. The mean particle size or average diameter of the microspheres significantly increased with increasing polymer concentration. Larger particles developed due to increased viscosity of the medium with an increasing higher polymeric concentration. This is because at higher viscosities there is enhanced interfacial tension and diminished shearing efficiency. Thus, the higher polymeric concentrated microspheres influence the particle size and drug release of the microspheres.

The surface morphology was observed by scanning electron microscopic photographs, which showed that the fabricated microspheres were spherical with a smooth in surface (figures 11, 12, 13).

The percentage yield and drug entrapment efficiency were determined for all the formulations. As the concentration of polymer increases both percentage yield and entrapment efficiency are also increased. The drug content was depends up on the concentration of polymers, as the concentration of polymer increases the drug content also increases due to the rapid dissolution of Poloxamer 407 in the receptor fluid.

The prepared microspheres then subjected to dissolution test for evaluating the *in-vitro* drug release studies. The result of dissolution studies indicates that cumulative percentage release of microspheres significantly increased with increasing polymer concentration. The increased density of the polymer matrix at higher concentration results in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres formed at a lower polymer concentration and having a larger surface area when exposed to the dissolution medium showed a faster drug release and the polymer concentration maintain the controlled drug release of the drug.

The data obtained for *in-vitro* release kinetics were fitted into equations for the zero-order, first-order, Higuchi and peppa's release models. The interpretation of the data was based on the value of the resulting regression coefficients. The *in-vitro* drug release showed the highest regression coefficient values for the zero order release kinetics, indicating that the polymer shows the controlled release of the drug, and the slope (n) value of peppa's mechanism of drug release was found to be non-fickian diffusion mechanism.

The release profile of formulations F5 and F6, were best fitting with USFDA guidelines for extended drug release for 12hrs, and release of the drug not more than 20% in 1^{st} hr and not less than 80% in 12^{th} hr.

Based on the parameters like drug content 98.16%, entrapment efficiency-89.36%, and the cumulative percentage drug release rate 93.85% at 12^{th} hrs, and follows zero order drug release kinetics and non-fickian diffusion mechanism. Hence the formulation F6 was considered as the best one among all the formulations.

11. CONCLUSION

The study concluded that Gliclazide microspheres can be developed with poloximer 407 polymer by Emulsion solvent diffusion-evaporation method and the results revealed that the formulation F6 shows desired release characteristics in the polymer ratio of (1:6) to achieve the controlled drug release of drug up to 12 hours. Further *in-vivo* studies to be carried out to confirm the formulation.

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